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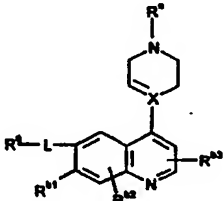
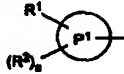
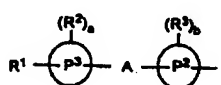
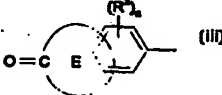
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(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).			
(72) Inventor; and (75) Inventor/Applicant (for US only): GASTER, Laramie, Mary [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).			
(74) Agent: WATERS, David, Martin; SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).			
(54) Title: QUINOLINEPIPERAZINE AND QUINOLINEPIPERIDINE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS COMBINED 5-HT <sub>1A</sub> , 5-HT <sub>1B</sub> AND 5-HT <sub>1D</sub> RECEPTOR ANTAGONISTS			
   			
(57) Abstract			
<p>The invention relates to compounds of formula (I) or a salt thereof in which R<sup>a</sup> is selected from a group of formula (i), (ii) or (iii); L is a group of formula -Y-C(=O)-DG- or -C(=O)-DG- or -DG-C(=O)- in which Y is -NH-, NR<sup>5</sup> where R<sup>5</sup> is C<sub>1</sub>-alkyl, or Y is -CH<sub>2</sub>- or -O-; D is nitrogen, carbon or a CH group, or G is hydrogen or C<sub>1</sub>-alkyl providing that D is nitrogen or a CH group, or G together with R<sup>b1</sup> forms a group W where W is (CR<sup>16</sup>R<sup>17</sup>)<sub>t</sub> where t is 2, 3 or 4 and R<sup>16</sup> and R<sup>17</sup> are independently hydrogen or C<sub>1</sub>-alkyl or W is (CR<sup>16</sup>R<sup>17</sup>)<sub>u</sub>-J where u is 0, 1, 2 or 3 and J is oxygen, sulphur, CR<sup>16</sup>=CR<sup>17</sup>, CR<sup>16</sup>=N, =CR<sup>16</sup>O, =CR<sup>16</sup>S or =CR<sup>16</sup>-NR<sup>17</sup> provided that u is not 0 when J is oxygen or sulphur; X is nitrogen or carbon; R<sup>b1</sup>, R<sup>b2</sup> and R<sup>b3</sup> are independently hydrogen, halogen, hydroxy, C<sub>1</sub>-alkyl, C<sub>2</sub>-alkenyl, C<sub>3</sub>-cycloalkyl, trifluoromethyl, C<sub>1</sub>-alkoxy or aryl, or R<sup>b1</sup> together with G forms a group W as defined above; R<sup>c</sup> is hydrogen or C<sub>1</sub>-alkyl; and <math>\text{---}</math> is a single bond when X is nitrogen or a single or double bond when X is carbon; having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS disorders.</p>			

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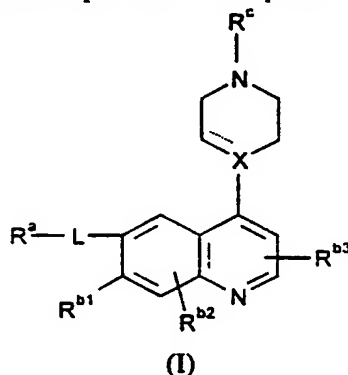
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**QUINOLINEPIPERAZINE AND QUINOLINEPIPERIDINE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS COMBINED 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub> AND 5-HT<sub>1D</sub> RECEPTOR ANTAGONISTS**

The present invention relates to novel piperazine derivatives, processes for their preparation, and pharmaceutical compositions containing them.

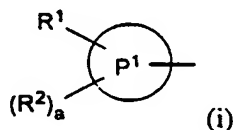
WO 95/04729, WO 95/06044 and WO 95/06637 all disclose a series of piperazine derivatives which are said to possess 5HT<sub>1D</sub> receptor antagonist activity. These compounds are alleged to be of use in the treatment of various CNS disorders such as depression. EPA 0533266/7/8 disclose a series of benzanilide derivatives which are said to possess 5-HT<sub>1D</sub> receptor antagonist activity. The 5-HT<sub>1D</sub> receptor was subsequently found to consist of a pair of gene products originally designated 5-HT<sub>1Dα</sub> and 5-HT<sub>1Dβ</sub> receptors which have more recently been reclassified as 5-HT<sub>1D</sub> and 5-HT<sub>1B</sub> receptors respectively. (Hartig, P.R. et al., Trends in Pharmacological Sciences 1992, Vol. 13, page 152, Hartig, P.R. et al., Trends in Pharmacological Sciences, 1996, Vol. 17, page 103).

A structurally distinct class of compounds have now been found that exhibit combined 5HT<sub>1A</sub>, 5HT<sub>1B</sub> and 5HT<sub>1D</sub> receptor affinity. It is expected that such compounds will be useful for the treatment and prophylaxis of various disorders. In a first aspect, the present invention therefore provides a compound of formula (I) or a salt thereof:



in which R<sup>a</sup> is selected from a group of formula (i), (ii) or (iii);

Group of formula (i)



R<sup>2</sup> is halogen, C<sub>1-6</sub>alkyl, C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub>cycloalkenyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkanoyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO<sub>2</sub>R<sup>10</sup>, CONR<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>R<sup>11</sup> where R<sup>10</sup> and R<sup>11</sup> are as defined above;

(ii)

Group of formula (iii)



The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The bicyclic aryl group represented by P<sup>1</sup>, P<sup>2</sup> and/or P<sup>3</sup>, which may be partially saturated, is preferably naphthyl.

Within the definition of R<sup>a</sup> formula (i) and (ii), examples of bicyclic heterocyclic rings represented by P<sup>1</sup>, P<sup>2</sup> and/or P<sup>3</sup> include isoquinoline, indole, benzofuran, benzothiophene, and most preferably quinoline. Examples of 5 to 7 membered heterocyclic rings represented by P<sup>1</sup>, P<sup>2</sup> and/or P<sup>3</sup>, include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrimidyl, pyrazinyl, and most preferably pyridyl. The heterocyclic and bicyclic heterocyclic groups listed above can be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom.

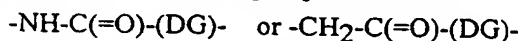
P<sup>1</sup> is preferably a phenyl, naphthyl or quinoline group. P<sup>2</sup> is preferably phenyl or naphthyl.

R<sup>1</sup> is preferably a halogen atom most preferably, fluorine, chlorine or bromine, and R<sup>2</sup> and/or R<sup>3</sup> are each preferably a halogen atom preferably, chlorine or bromine, or a C<sub>1</sub>-6 alkyl group for example a methyl group.

Within the definition of R<sup>a</sup> formula (ii), A is preferably a bond or oxygen.

Within the definition of R<sup>a</sup> formula (iii) the ring E, in addition to the keto group and the portion fused to the phenyl ring, is preferably formed from a straight chain alkylene grouping containing 2, 3 or 4 carbon atoms. The ring E is preferably a 5 or 6-membered ring in which the oxo group is advantageously attached to a carbon atom adjacent to the phenyl ring, the ring E being preferably attached to the 3,4-positions of the latter phenyl ring.

The group L is preferably a group of formula:-



in which D is preferably nitrogen and G is preferably a hydrogen atom or together with R<sup>b1</sup> forms a group W, preferably -(CH<sub>2</sub>)<sub>2</sub>- or -(CH<sub>2</sub>)<sub>3</sub>-.

R<sup>b1</sup>, R<sup>b2</sup> and R<sup>b3</sup> are preferably hydrogen or a halogen atom most preferably bromine or chlorine, or a C<sub>1</sub>-6 alkoxy group for example methoxy, or R<sup>b1</sup> together with G forms a group W referred to above.

X is preferably nitrogen.

R<sup>c</sup> is preferably a C<sub>1</sub>-6 alkyl group for example methyl.

Particularly preferred compounds according to the invention include:-

N-[3-Chloro-4-(pyridin-4-yl)phenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[4-(pyridin-4-yl)naphth-1-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[5-(pyridin-4-yl)naphth-1-yl]-urea  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[quinolin-6-yl]-urea,  
4-Bromo-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide.  
5-Bromo-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide.  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-4-(pyridin-4-yl)naphth-1-ylacetamide,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-5-(pyridin-4-yl)naphth-1-ylacetamide,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[4-(pyridin-4-yl)-3-trifluoromethylphenyl]-  
urea,  
N-[3-Cyano-4-(pyridin-4-yl)phenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[quinolin-5-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[quinolin-8-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[quinolin-3-yl]-urea,  
2,3-Dichloro-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide,  
5-(4-Acetylphenyl)-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[quinolin-4-yl]-urea,  
N-[3-Chloro-4-(pyridin-4-yl)phenyl]-N'-[4-(1-methylpiperidin-4-yl)quinolin-6-yl]-urea,  
N-[3-Methyl-4-(6-methylpyridin-2-yl)phenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-  
urea,  
N-[4-(2,6-Dimethylpyridin-4-yl)-3-methylphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-  
yl]-urea,  
N-[5-Cyanonaphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[5-(5-Methyl-1,2,4-oxadiazol-3-yl)naphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-  
yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[5-(pyrimidin-2-yloxy)naphth-1-yl]-urea,  
N-[5-Acetylnaphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[5-Bromonaphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[5-(6-Methylpyridin-2-yl)naphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[5-(2-Methylpyridin-5-yl)naphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[5-(2-Methylpyridin-3-yl)naphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[5-(pyrimidin-2-yl)naphth-1-yl]-urea,  
N-[5-Bromonaphth-1-yl]-N'-[4-(piperazin-1-yl)quinolin-6-yl]-urea,  
2,3-Dihydro-8-(4-methylpiperazin-1-yl)-1-[4-(pyridin-4-yl)naphth-1-  
ylaminocarbonyl]pyrrolo[2,3-g]quinoline.

2,3-Dihydro-8-(4-methylpiperazin-1-yl)-1-[5-(5-methyl-1,2,4-oxadiazol-3-yl)naphth-1-ylaminocarbonyl]pyrrolo[2,3-g]quinoline,  
2,3-Dihydro-8-(4-methylpiperazin-1-yl)-1-[5-(pyrimidin-2-yloxy)naphth-1-ylaminocarbonyl]pyrrolo[2,3-g]quinoline,  
9-(4-Methylpiperazin-1-yl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1,2,3,4-tetrahydropyrido[2,3-g]quinoline,  
9-(4-Methylpiperazin-1-yl)-1-[5-(pyrimidin-2-yloxy)naphth-1-ylaminocarbonyl]-1,2,3,4-tetrahydropyrido[2,3-g]quinoline,  
N-[8-Bromoquinolin-4-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[8-(2-Fluorophenyl)quinolin-4-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[8-(2-Methoxyphenyl)quinolin-4-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[2-Biphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[2,3-Dichlorophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N'-[4-Biphenyl]-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[3,4-Dichlorophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-Chlorophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[3-Cyanophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[4-phenoxyphenyl]-urea,  
N-[4-Bromophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-Acetylphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[2-Bromophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[3,5-Bis(trifluoromethyl)phenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[3-Acetylphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[2,6-Difluorophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[3-Bromophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[naphth-1-yl]-urea,  
N-[2,6-Dichlorophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-Chloro-2-methylphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-Bromo-3-methylphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-2-nitrophenylacetamide,  
4-Bromo-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-4-biphenylacetamide,  
3,4-Dichloro-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]benzamide,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]naphth-2-ylacetamide,  
4-Dimethylamino-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide,

3,4-Difluoro-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide,  
 N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-3-phenoxyphenylacetamide.  
 N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylcarboxamide.  
 N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-4-phenoxybenzamide,  
 N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl]-  
 urea,  
 N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[5-oxoindan-2-yl]-urea.  
 2,3-Dihydro-8-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-  
 naphthalenyl)aminocarbonyl]pyrrolo[2,3-g]quinoline,  
 9-(4-Methylpiperazin-1-yl)-1-[(5-oxo-5,6,7,8-tetrahydronaphth-6-yl)aminocarbonyl]-1,2,3,4-  
 tetrahydropyrido[2,3-g]quinoline  
 or pharmaceutically acceptable salts thereof.

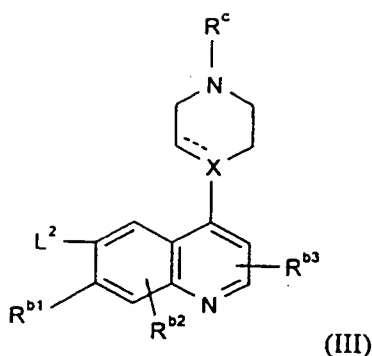
Preferred salts of the compounds of formula (I) are pharmaceutically acceptable salts. These include acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and the mixtures thereof including racemates.

Compounds of the invention can be prepared using procedures known in the art. In a further aspect the present invention provides a process for the preparation of a compound of formula (I) which comprises

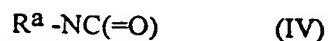
- (a) where L is  $\text{-C(=O)-DG -}$  or  $\text{-DG-C(=O)-}$ , coupling a compound of formula (II):  

$$\text{Ra-L}^1 \quad \text{(II)}$$
  
 with a compound of formula (III):

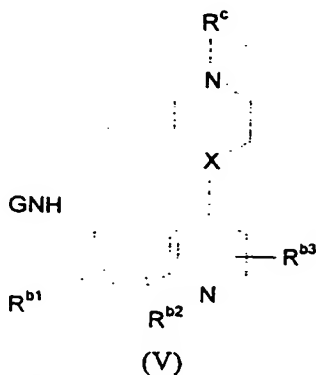


in which  $R^a$ ,  $R^{b1}$ ,  $R^{b2}$ ,  $R^{b3}$ ,  $R^c$  and  $X$  are as defined in formula (I) and  $L^1$  and  $L^2$  contain the appropriate functional groups which are capable of reacting together to form the  $L$  moiety; or

(b) where  $L$  is  $-Y-C(=O)-DG$  in which  $D$  is nitrogen and  $Y$  is  $NH$ , coupling a compound of formula (IV):

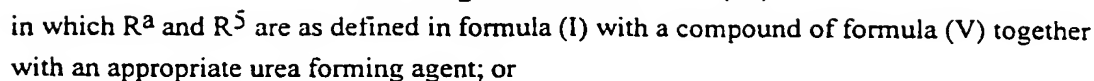


in which  $R^a$  is as defined in formula (I) or a protected derivative thereof, with a compound of formula (V):

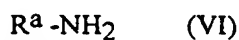


in which  $R^{b1}$ ,  $R^{b2}$ ,  $R^{b3}$ ,  $R^c$ ,  $G$  and  $X$  are as defined in formula (I), or a protected derivative thereof; or

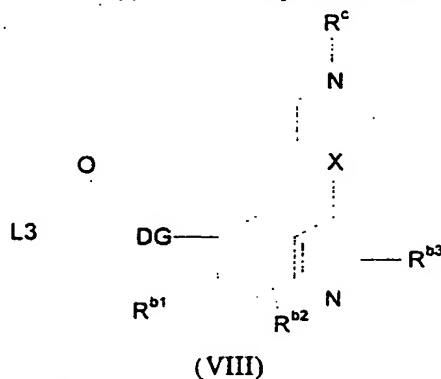
(c) where  $L$  is  $-Y-C(=O)-DG$  in which  $D$  is nitrogen and  $Y$  is  $NH$  or  $NR^5$ , reacting a compound of formula (VI)


$$\text{R}^a - \text{Y} - (\text{C}=\text{O}) - \text{L}^3 \quad (\text{VII})$$

(e) where L is -Y-C(=O)-DG- in which D is CH and Y is NH, reacting a compound of formula (VI):



in which R<sup>a</sup> is as defined in formula (I) with a compound of formula (VIII):



- removing any protecting groups,
- converting a compound of formula (I) into another compound of formula (I),
- forming a pharmaceutically acceptable salt.

$L^1$  is  $NH_2$  and  $L^2$  is  $CO_2^{2-}$

in which  $L^a$  is an appropriate leaving group.

Suitably one of  $L^1$  and  $L^2$  is an activated carboxylic acid derivative such as an acyl chloride or acid anhydride, and the other is an amine group. Activated compounds of formulae (II) and (III) can also be prepared by reaction of the corresponding carboxylic acid with a coupling agent such as dicyclohexylcarbodiimide, carbonyldiimidazole or diphenylphosphoryl azide. Preferably  $L^1$  or  $L^2$  is a group  $COL^a$  where  $L^a$  is halo particularly chloro.

Compounds of formulae (II) and (III) are typically reacted together in an inert solvent such as dimethylformamide, tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as an alkali metal hydroxide, triethylamine or pyridine.

The reaction in process (b) is conveniently effected in an organic solvent such as dichloromethane.

In process (c) the urea forming agent can be carbonyl diimidazole, triphosgene or phosgene, and carried out in an inert organic solvent such as dimethylformamide, tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

In process (d) the leaving group  $L^3$  may be a halogen e.g. chloro group and the reaction may be carried out in an inert organic solvent such as tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

In process (e) the leaving group  $L^3$  may be a halogen e.g. chloro group and the reaction may be carried out in an inert organic solvent such as tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques. For example, in the case wherein  $R^C$  is hydrogen, it is possible to introduce a  $C_{1-6}$ alkyl group by conventional alkylation using 1 molar equivalent of a  $C_{1-6}$ alkyl halide and 1 molar equivalent of a suitable base in an inert solvent.

Intermediate compounds of formula (II) to (VIII) can be prepared using standard procedures known in the art.

It will be appreciated to those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques can be used. For example, primary amines can be protected as

phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. These groups can be removed by conventional procedures well known in the art.

Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection is achieved using standard conditions.

The involvement of serotonin receptors in a number of pharmacological effects has been reviewed by R. A. Glennon in "Serotonin Receptors: Clinical Implications", Neuroscience and Behavioural Reviews, 1990, 14, 35 and by L.O. Wilkinson and C.T. Dourish in "Serotonin Receptor Subtypes : Basic and Clinical Aspects" S. Peroutka Ed., John Wiley and Sons, New York, 1991 p.147.

Serotonin (5-hydroxytryptamine; 5HT) receptors have been implicated in a number of pharmacological effects including mood disorders including depression, seasonal affective disorder and dysthymia, anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnesic disorders and age-associated memory impairment; disorders of eating behaviours, including anorexia nervosa and bulimia nervosa, sleep disorders (including disturbances of Circadian rhythm), motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders. Serotonin receptor ligands have been shown to be of use in the treatment of emesis and nausea and may also be of use in endocrine disorders such as hyperlactinaemia, vasospasm (particularly in the cerebral vasculature), cerebellar ataxia and hypertension, as well as disorders of the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction and hypothermia.

Ligands with high affinity for the 5HT<sub>1</sub> receptors are well recognised as having therapeutic utility for the treatment of the above conditions. For example: WO 95/31988 refers to the use of a 5-HT<sub>1D</sub> receptor antagonist in conjunction with a 5-HT<sub>1A</sub> receptor antagonist to treat CNS (central nervous system), endocrine and GI (gastrointestinal) disorders; K. Rasmussen (Annual Reports in Medicinal Chemistry, (1995) 30, 1) describes the utility of 5-HT<sub>1A</sub> receptor agonists and partial agonists in the treatment of various CNS disorders; P. Trouillas (Progress in Brain Research, C.I. de Zeeuw, P. Stara and J. Voogd, Eds. 1997, 144, 589) and G. Maura (J. Neurochemistry, 1996, 66, 202) propose that administration of agonist ligands selective for the 5-HT<sub>1A</sub> receptor or for both 5-HT<sub>1A</sub> and 5-HT<sub>1D</sub> receptors should provide effective treatment for human cerebellar ataxias.

The present invention also provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

In a further aspect the invention provides a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof.

In particular the invention provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

The affinities of the compounds of this invention for the 5HT<sub>1A</sub>, 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors can be determined by the following radioligand binding assay. HEK 293 cells expressing 5-HT<sub>1A</sub> receptors ( $4 \times 10^7$ /ml) are homogenised in Tris buffer and stored in 1ml aliquots. CHO cells expressing 5-HT<sub>1B</sub> receptors ( $4 \times 10^7$  cells/ml) are homogenised in Tris buffer and stored in 1.5 ml aliquots. CHO cells expressing 5-HT<sub>1D</sub> receptors ( $0.563 \times 10^8$ /ml) are homogenised in Tris buffer and stored in 1 ml aliquots.

0.4 ml of a cell suspension is incubated with [<sup>3</sup>H]-5-HT (4nM) for 5-HT<sub>1B/1D</sub> receptors and [<sup>3</sup>H]-8-OH DPAT (1nM) for 5-HT<sub>1A</sub> receptors in Tris Mg HCl buffer (pH 7.7) and test drug, at 37°C for 45 minutes. Each test drug is tested at 10 concentrations (0.01 mM to 0.3 nM final concentration), with non-specific binding defined using 0.01 mM 5-HT. The total assay volume is 0.5 ml. Incubation is stopped by rapid filtration using a Packard Filtermate (filters pre-soaked in 0.3% polyethylenimine) and radioactivity measured by Topcount scintillation counting. pK<sub>i</sub> values are calculated from the IC<sub>50</sub> generated by an iterative least squares curve fitting programme.

The intrinsic activity of the compounds of this invention can be determined according to the following procedure. HEK293 cell membranes stably expressing human 5-HT<sub>1A</sub> receptors and CHO cell membranes stably expressing human 5-HT<sub>1B</sub> receptors are homogenised in HEPES/EDTA buffer and stored in 1ml aliquots, and [<sup>35</sup>S]GTPγS binding studies are carried out essentially as described by Lazareno *et al.*, (Life Sci., 1993, 52, 449) with some minor modifications. Membranes from  $10^6$  cells are pre-incubated at 30°C for 30 min in 20 mM HEPES buffer (pH 7.4) in the presence of MgCl<sub>2</sub> (3 mM), NaCl (100 mM), GDP (10 μM) and ascorbate (0.2 mM), with or without compounds. The reaction is started by the addition of 10 μl of [<sup>35</sup>S]GTPγS (100 pM, assay concentration) followed by a further 30 minutes incubation at 30°C. Non-specific binding was determined using non-radiolabelled GTPγS (20 μM) added prior to the membranes. The reaction is terminated by

rapid filtration through Whatman GF/B grade filters followed by 5 x 1 ml washes with ice cold HEPES (20 mM) /MgCl<sub>2</sub> (3 mM) buffer. Radioactivity is measured using liquid scintillation spectrometry. This procedure is hereafter referred to as the [<sup>35</sup>S]GTPγS functional assay.

The compounds of formula (I) show high affinity for the 5HT<sub>1A</sub>, 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors. It has been found, using the [<sup>35</sup>S]GTPγS functional assay, that certain compounds of formula (I) show varying levels of intrinsic efficacy, which is defined by a scale ranging from 1.0 to 0 (1 defines the maximum response elicited by the agonist 5-HT, 0 defines antagonism). The difficulties in describing intrinsic activity of drugs acting at G protein coupled receptors is recognised in the art (Hoyer and Boddeke, Trends in Pharmacological Sciences, July 1993, [Vol. 14], page 270-275). We believe that however these ligands are classified according to this functional assay, the compounds of this invention will be useful antidepressants *in vivo*. It is believed that the preferred compounds of this invention will display 5HT<sub>1A</sub>, 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> antagonist activity *in vivo* and that such compounds will have a rapid onset of action. A rapid onset of action is particularly advantageous for antidepressant compounds: by 'rapid onset of action' we mean that a therapeutic response is seen within 7 days from first administration of the compound, as opposed to a period of about 21 days or more which is typical of SSRI's, tricyclic antidepressants and buspirone.

Compounds of formula (I) which have an intrinsic activity of 0.5 or less in the [<sup>35</sup>S]GTPγS functional assay are particularly preferred, as these compounds are more likely to be full antagonists *in vivo*. As disclosed in WO 95/31988, the simultaneous antagonism of pre-synaptic 5HT<sub>1A</sub>/1B/1D receptors will result in increased release of 5HT *in vivo* and this will improve 5HT neurotransmission.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, a selective serotonin reuptake inhibitor (SSRI) antidepressant.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or

infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Examples illustrate the preparation of compounds of the invention.

**Description 1****4-(4-Methylpiperazin-1-yl)-6-nitroquinoline (D1)**

4-Chloro-6-nitroquinoline (J. Org. Chem. 1944, 9, 302) (2.08g, 0.01mol) and 4-methylpiperazine (1.00g, 0.01mol) were stirred together in DMF (20ml). Triethylamine (2ml) was added and the mixture was stirred at 50°C under argon for 16hours. The solvent was evaporated *in vacuo* and the residue partitioned between 20% aqueous K<sub>2</sub>CO<sub>3</sub> and dichloromethane. The organic phase was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give an oil, which was purified by chromatography on silica using methanol/dichloromethane to give the title compound (2.03g, 75%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 9.0 (d, 1H), 8.82 (d, 1H), 8.40 (dd, 1H), 8.24 (d, 1H), 6.95 (d, 1H), 3.35 (m, 4H), 2.75 (m, 4H), 2.46 (s, 3H). MS: m/z = 273 (MH<sup>+</sup>).

**Description 2****6-Amino-4-(4-methylpiperazin-1-yl)quinoline (D2)**

4-(4-Methylpiperazin-1-yl)-6-nitroquinoline (D1, 1.92g, 7.05mmol) was dissolved in ethanol (70ml), Raney nickel (0.1g) was added and the mixture hydrogenated at room temperature and atmospheric pressure until the uptake of hydrogen had ceased. The catalyst was removed by filtration and the filtrate evaporated *in vacuo* to yield the title compound as an oil (1.59g, 93%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 8.45 (d, 1H), 7.85 (dd, 1H), 7.18 (m, 2H), 6.79 (d, 1H), 3.98 (s, 2H), 3.19 (m, 4H), 2.66 (m, 4H), 2.41 (s, 3H). MS: m/z = 243 (MH<sup>+</sup>).

**Description 3****3-Chloro-4-(pyridin-4-yl)acetanilide (D3)**

4-Bromo-3-chloroacetanilide (8.0g, 32.2mmol) in dimethoxyethane (300ml) and water (200ml) was treated with pyridin-4-ylboronic acid (4g, 32mmol) and Na<sub>2</sub>CO<sub>3</sub> (10.24g, 97mmol) and the reaction degassed by bubbling argon through the mixture for 30 minutes. The reaction was then treated with tetrakis(triphenylphosphine)palladium (0) and refluxed under argon for 24 hours. The reaction was concentrated *in vacuo* to low volume and the residue partitioned between 5M HCl and dichloromethane. The aqueous layer was separated and carefully neutralised with 2M NaOH and the resulting solid collected by filtration to give the title compound (5.0g, 63%).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>DMSO) δ (ppm): 10.45 (s, 1H), 8.7 (d, 2H), 8.05 (s, 1H), 7.65 (d, 1H), 7.55 (d, 2H), 7.5 (d, 1H), 2.2 (s, 3H).

**Description 4****3-Chloro-4-(pyridin-4-yl)aniline (D4)**

3-Chloro-4-(pyridin-4-yl)acetanilide (D3, 5g, 20.3mmol) in 2M NaOH (100ml) and ethanol (100ml) was heated at reflux under argon for 36 hours. The reaction was then concentrated *in vacuo* to remove the ethanol and the product recovered by extraction into CH<sub>2</sub>Cl<sub>2</sub>. The organic extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo* to afford the title compound (3.5g, 84%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 8.65 (d, 2H), 7.35 (d, 2H), 7.15 (d, 1H), 6.8 (s, 1H), 6.65 (s, 1H), 3.95 (br s, 2H).

**Description 5****4-(Pyridin-4-yl)-1-naphthylamine (D5)**

The title compound was prepared from 4-bromo-1-naphthylamine and pyridin-4-ylboronic acid using a similar procedure to Description 3 as a yellow crystalline solid (78%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.68 (d, 2H), 7.90 (d, 2H), 7.30 (m, 5H), 6.84 (d, 1H), 4.32 (s, 2H)

**Description 6****5-(Pyridin-4-yl)-1-naphthylamine (D6)**

The title compound was prepared from 5-bromo-1-naphthylamine (JP 08151353A2) and pyridin-4-ylboronic acid using a similar procedure to Description 3 as a yellow solid (61%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.75 - 8.67 (m, 2H), 7.93 (d, 1H), 7.70 - 7.35 (m, 4H), 7.28 - 7.20 (m, 2H), 6.85 - 6.80 (m, 1H), 4.25 (s, 2H).

**Description 7****4-(Pyridin-4-yl)-3-trifluoromethylacetanilide (D7)**

The title compound was prepared from 4-bromo-3-trifluoromethylacetanilide and pyridin-4-ylboronic acid using a similar procedure to Description 3 (59%).

<sup>1</sup>H NMR (250MHz CDCl<sub>3</sub>) δ (ppm): 8.65(d, 2H), 8.4 (s, 1H), 7.9(m, 2H), 7.3(m, 3H), 2.25(s, 3H).

**Description 8****4-(Pyridin-4-yl)-3-trifluoromethylaniline (D8)**

The title compound was prepared from 4-(pyridin-4-yl)-3-trifluoromethylacetanilide (D7) using a similar procedure to Description 4 (95%).

$^1\text{H}$  NMR (250MHz  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.6(m, 2H), 7.25(m, 2H) 7.05 (m, 2H), 6.85 (m, 1H), 4.0 (s, 2H).

#### Description 9

##### 4-Chloro-3-cyanoaniline (D9)

2-Chloro-5-nitrobenzonitrile (18.2g, 100 mmol) in ethanol (500ml) at reflux under an atmosphere of argon was treated over 30 minutes with tin (II) chloride (75.6g, 400 mmol). The exothermic reaction required little additional heating. After cooling, the reaction mixture was concentrated *in vacuo* to a gum, which was partitioned between NaOH solution and  $\text{CH}_2\text{Cl}_2$ . The organic phase was separated, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo* to a gum, which was chromatographed on silica gel eluting with 3-10% MeOH/ $\text{CH}_2\text{Cl}_2$  to give the title compound as needles (6.5g, 43%), mp 124-126°C.

$^1\text{H}$  NMR (250MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.25 (d, 1H), 6.95 (s, 1H), 6.8 (d, 1H), 4.0 (br s, 2H).

#### Description 10

##### 3-Cyano-4-(pyridin-4-yl)aniline (D10)

The title compound was prepared from 4-chloro-3-cyanoaniline (D9) and pyridin-4-ylboronic acid using a similar procedure to Description 3. The crude product was purified by chromatography on silica gel eluting with ethyl acetate to give needles from ether (8%), mp 131-133°C.

$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.7 (d, 2H), 7.45 (d, 2H), 7.35 (d, 1H), 7.05 (s, 1H), 6.95 (d, 1H), 4.1 (br s, 2H).

#### Description 11

##### 2,3-Dichlorophenylacetonitrile (D11)

A stirred suspension of 2,3-dichlorobenzyl chloride (20g, 0.10 mol) in ethanol (140ml) and water (10ml) was treated with sodium cyanide (6g, 0.12 mol) in water (25ml), heated under reflux for 8 hours and then left to stand overnight. The reaction mixture was concentrated *in vacuo* and partitioned between dichloromethane and aqueous  $\text{K}_2\text{CO}_3$  solution. The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ), concentrated *in vacuo*, washed with petroleum ether and dried *in vacuo* to afford the title compound (14.59g, 77%).

$^1\text{H}$  NMR (250 MHz  $\text{CDCl}_3$ )  $\delta$ (ppm) : 7.56-7.39 (m, 2H), 7.32-7.15 (m, 1H), 3.91 (s, 2H).

#### Description 12

##### Ethyl 2,3-dichlorophenylacetate (D12)

A stirred suspension of 2,3-dichlorophenylacetonitrile (D11, 14g, 75 mmol) in ethanol (200ml) was treated with concentrated sulphuric acid (20ml) and heated under reflux for 3 days. The reaction mixture was then concentrated *in vacuo* and partitioned between dichloromethane and water. The organic layer was separated, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo* to afford the title compound (16.45g, 94%).

$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm) : 7.4-7.3 (m, 1H), 7.2-7.15 (m, 2H), 4.20-4.18 (q, 2H), 3.75 (s, 2H), 1.27-1.15 (t, 3H)

#### Description 13

##### 2,3-Dichlorophenylacetic acid (D13)

A stirred suspension of ethyl 2,3-dichlorophenylacetate (D12, 4.4g, 19 mmol) in 5M HCl acid (300 ml) was heated under reflux overnight. The reaction mixture was concentrated *in vacuo* to afford the title compound (2.5g, 65%).

$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm) 7.45-7.36 (m, 1H), 7.23-7.12 (m, 2H), 3.85 (s, 2H).

#### Description 14

##### 6-Nitro-4-(pyridin-4-yl)quinoline (D14)

The title compound was prepared from 4-chloro-6-nitroquinoline (J. Org. Chem. 1944, 9, 302) and pyridin-4-ylboronic acid using a similar procedure to Description 3 (63%).

$^1\text{H}$  NMR (250MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 9.2 (d, 1H), 8.9 (d, 2H), 8.8 (s, 1H), 8.55 (dd, 1H), 8.35 (d, 1H), 7.5 (d, 1H), 7.45 (d, 2H).

#### Description 15

##### 1-Methyl-4-(6-nitroquinolin-4-yl)pyridinium iodide (D15)

6-Nitro-4-(pyridin-4-yl)quinoline (D14, 500mg, 2 mmol) in acetone (100ml) was treated with iodomethane (2.8g, 20mmol) and the reaction heated under reflux for 2 hours, then cooled to room temperature. The title compound which precipitated was collected by filtration (610mg, 80%).

$^1\text{H}$  NMR (250 MHz,  $\text{d}^6\text{DMSO}$ )  $\delta$  (ppm): 9.35 (d, 1H), 9.25 (d, 2H), 8.65 (s, 1H), 8.6 (d, 1H), 8.5 (d, 2H), 8.45 (d, 1H), 7.9 (d, 1H), 4.5 (s, 3H).

#### Description 16

##### 6-Amino-4-(1-methylpiperidin-4-yl)quinoline hydroiodide (D16)

1-Methyl-4-(6-nitroquinolin-4-yl)pyridinium iodide (D15, 300mg, 0.78 mmol) in methanol (25ml) was treated with platinum dioxide (150ml) and the suspension stirred under an

atmosphere of hydrogen for 4 hours. The reaction was then filtered through Kieselghur and concentrated *in vacuo* to give a green oil (300mg).

<sup>1</sup>H NMR (250MHz, CD<sub>3</sub>OD) δ (ppm): 8.3 (d, 1H), 7.65 (d, 1H), 7.25 (s, 1H), 7.15 (d, 1H), 7.1 (d, 1H), 3.5-3.2 (3H, m), 3.05-2.9 (m, 2H), 2.65(s, 3H), 2.1-1.75 (m, 4H). NH<sub>2</sub> not observed.

#### Description 17

##### 4-Amino-2-methylphenylboronic acid (D17)

A stirred solution of 4-bromo-3-methylaniline (20g, 0.107 mol) and triethylamine (33ml, 0.237 mol) in dichloromethane (250ml) at 0°C under argon was treated dropwise over 15 minutes with a solution of bis(chlorodimethylsilyl)ethane (25.3g, 0.12 mol) in dichloromethane (100ml). The mixture was warmed to room temperature and stirred for 20 hours, then filtered and concentrated *in vacuo*. The residue was extracted with 60-80 petrol (400ml) and the filtrate concentrated *in vacuo* to leave the stabase as an orange oil (35g, 100%). This was dissolved in dry THF (400ml), cooled to -65°C under argon and treated dropwise over 15 min with 2.5M n-butyllithium in hexane (52ml, 0.13mol). The mixture was stirred at -65°C for 1 hour, then treated dropwise over 10 min with triisopropylborate (30ml, 0.13 mol), stirred at -65°C for a further 1.5 hours, then treated with saturated aqueous NH<sub>4</sub>Cl solution (100ml) and allowed to warm to room temperature. The mixture was diluted with water (200ml), acidified with conc. HCl acid (50ml), stirred for 20 min, then concentrated under vacuum to approx. 400ml volume. The aqueous residue was washed with ethyl acetate and then basified by addition of solid K<sub>2</sub>CO<sub>3</sub>. The basic mixture was extracted with ethyl acetate and the extract dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to approx. 150ml volume, when a solid began to precipitate out. The mixture was cooled to 8°C and the solid filtered off and dried to afford the title compound as a white solid (9.2g, 51%).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>DMSO) δ (ppm): 7.69 (d, 1H), 6.40-6.32 (m, 2H), 5.34 (br s, 2H), 2.52 (s, 3H). Acid protons not observed.

#### Description 18

##### 3-Methyl-4-(6-methylpyridin-2-yl)aniline (D18)

The title compound was prepared from 2-bromo-6-methylpyridine and 4-amino-2-methylphenylboronic acid (D17) using a similar procedure to Description 3 as beige solid (100%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 7.62-7.55 (m, 1H), 7.22 (d, 1H), 7.15 (d, 1H), 7.05 (d, 1H), 6.62-6.55 (m, 2H), 3.68 (br s, 2H), 2.59 (s, 3H), 2.31 (s, 3H).

**Description 19****4-(2,6-Dimethylpyridin-4-yl)-3-methylaniline (D19)**

The title compound was prepared from 4-chloro-2,6-dimethylpyridine (Chem. Abs. 1952, 46, 4541) and 4-amino-2-methylphenylboronic acid (D17) using a similar procedure to Description 3 as beige solid (4%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 7.01 (d, 1H), 6.90 (s, 2H), 6.62-6.54 (m, 2H), 3.70 (br s, 2H), 2.55 (s, 6H), 2.22 (s, 3H).

**Description 20****5-Nitronaphth-1-ylamidoxime (D20)**

A stirred solution of sodium hydroxide (0.44g, 11 mmol) in methanol (100ml) was treated with hydroxylamine hydrochloride (0.76g, 11 mmol). The mixture was gently warmed and then 5-nitronaphth-1-ylcarbonitrile (EP 456090) was added and the resultant mixture heated at reflux for 36 hours. The cooled mixture was concentrated *in vacuo* to 10ml, water (50ml) was added and the precipitate collected by filtration, washed with water and dried *in vacuo* to afford the title compound as a pale yellow powder (1.12g, 88%).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>DMSO) δ (ppm): 9.74 (s, 1H), 8.67 (d, 1H), 8.33 (m, 2H), 7.76-7.70 (m, 3H), 6.15 (s, 2H).

**Description 21****5-Methyl-3-(5-nitronaphth-1-yl)-1,2,4-oxadiazole (D21)**

A stirred solution of 5-nitronaphth-1-ylamidoxime (D20, 1.28g, 5.5mmol) in pyridine (10ml) was treated with acetyl chloride (0.78ml, 11 mmol). The mixture was stirred at room temperature for 0.5 hours, then heated at reflux for 24 hours. The cooled mixture was poured into water (100ml) and extracted with ethyl acetate (3 x 25ml). The combined extract was washed with dilute HCl acid and water, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to dryness *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>. The title compound was isolated as a pale yellow solid (0.86g, 61%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 9.27 (d, 1H), 8.67 (d, 1H), 8.34 (d, 1H), 8.20 (d, 1H), 7.81 (dd, 1H), 7.68 (dd, 1H), 2.75 (s, 3H).

**Description 22****5-(5-Methyl-1,2,4-oxadiazol-3-yl)-1-naphthylamine (D22)**

A stirred suspension of 5-methyl-3-(5-nitronaphth-1-yl)-1,2,4-oxadiazole (D21, 100mg, 0.4mmol) in ethanol (8ml) and water (4ml) was treated with iron powder (110mg, 1.96mmol) and ammonium chloride (11mg, 0.21mmol) and the mixture heated to reflux for 1 hour. The mixture was cooled, filtered through celite and the filtrate concentrated to dryness. The residue was dissolved in ethyl acetate (25ml), washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to dryness. The title compound was isolated as its hydrochloride salt as a yellow/green solid (110mg, 85%).

$^1\text{H}$  NMR (HCl salt) (250MHz,  $\text{d}^6\text{DMSO}$ )  $\delta$  (ppm): 8.73 (t, 1H), 8.10 (d, 1H), 7.94 (d, 1H), 7.60 (t, 1H), 7.41 (d, 2H), 2.47 (s, 3H). Amine signal obscured by water peak.

#### Description 23

##### 5-(Pyrimidin-2-yloxy)-1-naphthylamine (D23)

A stirred mixture of 5-hydroxy-1-naphthylamine (0.51g, 3mmol), 2-bromopyrimidine (0.48g, 3mmol) and anhydrous potassium carbonate (0.41g, 3mmol) in dry DMF (5ml) was heated to 110°C under argon for 4 hours. The mixture was concentrated to dryness *in vacuo* and the residue treated with water (30ml) and extracted with ethyl acetate (3 x 30ml). The combined extract was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to dryness *in vacuo*. The residue was triturated with ether to afford the title compound as a pale buff solid (0.41g, 58%).

$^1\text{H}$  NMR (250MHz,  $\text{d}^6\text{DMSO}$ )  $\delta$  (ppm): 8.55 (d, 2H), 7.75 (d, 1H), 7.48 (t, 1H), 7.39-7.18 (m, 3H), 7.02 (t, 1H), 6.78 (d, 1H), 4.13 (s, 2H).

#### Description 24

##### 5-Acetyl-1-naphthylamine (D24)

A stirred solution of 5-nitro-1-acetonaphthone (Aust. J. Chem., 1995, 48, 1969) (0.75g, 3.5mmol) and 10% Pd-C (0.20g) in cyclohexene (10ml) and methanol (75ml) was heated at reflux for 6h. The cooled mixture was filtered, concentrated to dryness *in vacuo* and the residue dissolved in  $\text{CH}_2\text{Cl}_2$  (50ml), washed with water (20ml), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to dryness. The residue was triturated in diethyl ether/hexane to afford the title compound as yellow/brown solid (0.52g, 80%).

$^1\text{H}$  NMR (250MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.03 (t, 2H), 7.83 (dd, 1H), 7.49-7.36 (m, 2H), 6.82 (d, 1H), 4.17 (s, 2H), 2.73 (s, 3H).

#### Description 25

##### 5-Bromonaphth-1-yl isocyanate (D25)

The title compound was prepared from 5-bromo-1-naphthoic acid (Bull. Soc. Chim. Fr., 1968, 7, 2957) using a similar procedure to Description 28. The isocyanate was not isolated, but used in the next step as its toluene solution.

#### Description 26

##### 5-Carboxynaphth-1-ylboronic acid (D26)

A stirred solution of 5-bromo-1-naphthoic acid (Bull. Soc. Chim. Fr., 1968, 7, 2957) (22.3g, 0.089 mol) in dry THF (1000ml) at -60°C under argon was treated dropwise over 15 minutes with 1.6M n-butyllithium in hexane (125ml, 0.20 mol). The initial brown solution gave a beige precipitate as the first equivalent was added, which redissolved on addition of the second equivalent. The resulting solution was stirred at -60°C for 40 minutes, then triisopropylborate (51ml, 0.22 mol) was added, and the mixture stirred at -60°C for a further 1h. before warming gradually to -10°C. Saturated aqueous  $\text{NH}_4\text{Cl}$  solution (300ml) was added, followed by water (400ml) and then 5M HCl acid (200ml). The resulting mixture was concentrated *in vacuo* to approx. 1000ml volume, then basified by addition of 40% NaOH solution and washed with ethyl acetate. The aqueous was added to excess 5M HCl acid and the solid which precipitated out was filtered off, washed with water and dried to afford a white solid (9.67g), which contained approx. 50% of the title compound together with 1-naphthoic acid.

#### Description 27

##### 5-(6-Methylpyridin-2-yl)-1-naphthoic acid (D27)

The title compound was prepared from 2-bromo-6-methylpyridine and 5-carboxynaphth-1-ylboronic acid (D26) using a similar procedure to Description 3 as beige solid (46%).  
 $^1\text{H}$  NMR (250MHz,  $\text{d}^6\text{DMSO}$ )  $\delta$  (ppm): 8.90 (d, 1H), 8.13 (d, 1H), 8.06 (dd, 1H), 7.84 (t, 1H), 7.67 (t, 1H), 7.62-7.46 (m, 2H), 7.41 (d, 1H), 7.32 (d, 1H), 2.55 (s, 3H). Acid proton not observed.

#### Description 28

##### 5-(6-Methylpyridin-2-yl)naphth-1-yl isocyanate (D28)

A suspension of 5-(6-methylpyridin-2-yl)-1-naphthoic acid (D27, 400mg, 1.5 mmol) in dichloromethane (25ml) was treated with oxalyl chloride (0.26ml, 3.0 mmol) and stirred at room temperature for 20 hours, then concentrated *in vacuo*. The residue was suspended in dichloromethane (30ml) and shaken quickly with ice-cold  $\text{NaHCO}_3$  solution (20ml). The organic solution was immediately separated and added to a stirred solution of sodium azide

(195mg, 3.0 mmol) and tetrabutylammonium iodide (35mg) in water (15ml) at 5°C. The mixture was stirred well at 0-5°C for 1 hour, then diluted with water (20ml) and extracted with dichloromethane. The extract was dried ( $\text{Na}_2\text{SO}_4$ ) and cautiously concentrated under vacuum at room temperature to approx. 10ml volume. This solution was then treated with toluene (30ml) and gently heated under argon to reflux temperature and maintained for 0.5 hours. The reaction mixture was allowed to cool and the isocyanate solution used directly in the next step.

#### **Description 29**

##### **5-(2-Methylpyridin-5-yl)-1-naphthoic acid (D29)**

The title compound was prepared from 5-bromo-2-methylpyridine and 5-carboxynaphth-1-ylboronic acid (D26) using a similar procedure to Description 3 as beige solid (64%).

$^1\text{H}$  NMR (250MHz,  $\text{d}^6\text{DMSO}$ )  $\delta$  (ppm): 13.3 (br s, 1H), 8.90 (d, 1H), 8.53 (s, 1H), 8.15 (d, 1H), 7.93 (d, 1H), 7.83-7.67 (m, 2H), 7.62-7.47 (m, 2H), 7.43 (d, 1H), 2.57 (s, 3H).

#### **Description 30**

##### **5-(2-Methylpyridin-5-yl)naphth-1-yl isocyanate (D30)**

The title compound was prepared from 5-(2-methylpyridin-5-yl)-1-naphthoic acid (D29) using a similar procedure to Description 28. The isocyanate was not isolated, but used in the next step as its toluene solution.

#### **Description 31**

##### **5-(2-Methylpyridin-3-yl)-1-naphthoic acid (D31)**

The title compound was prepared from 2-methyl-3-iodopyridine and 5-carboxynaphth-1-ylboronic acid (D26) using a similar procedure to Description 3 as beige solid (61%).

$^1\text{H}$  NMR (250MHz,  $\text{d}^6\text{DMSO}$ )  $\delta$  (ppm): 13.3 (br s, 1H), 8.91 (d, 1H), 8.59 (dd, 1H), 8.15 (dd, 1H), 7.78-7.69 (m, 1H), 7.64 (dd, 1H), 7.60-7.45 (m, 3H), 7.43-7.35 (m, 1H), 2.13 (s, 3H).

#### **Description 32**

##### **5-(2-Methylpyridin-3-yl)naphth-1-yl isocyanate (D32)**

The title compound was prepared from 5-(2-methylpyridin-3-yl)-1-naphthoic acid (D31) using a similar procedure to Description 28. The isocyanate was not isolated, but used in the next step as its toluene solution.

#### **Description 33**

**5-(Pyrimidin-2-yl)-1-naphthoic acid (D33)**

The title compound was prepared from 2-bromopyrimidine and 5-carboxynaphth-1-ylboronic acid (D26) using a similar procedure to Description 3 to afford the product as an off-white solid.

<sup>1</sup>H NMR (250 MHz, d<sup>6</sup>DMSO)  $\delta$  (ppm): 13.15 (br, 1H), 9.05 (d, 1H), 8.98 (d, 1H), 8.88 (d, 1H), 8.70 (d, 1H), 8.15 (m, 1H), 8.04 (m, 1H), 7.75 (t, 1H), 7.60 (m, 2H).

**Description 34****5-(Pyrimidin-2-yl)naphth-1-yl isocyanate (D34)**

The title compound was prepared from 5-(pyrimidin-2-yl)-1-naphthoic acid (D33) using a similar procedure to Description 28. The isocyanate was not isolated, but used in the next step as its toluene solution.

**Description 35****1-Benzyl-5-nitroindoline (D35)**

To a stirred solution of 5-nitroindoline (50g, 0.30mol) in acetone (500ml) was added anhydrous potassium carbonate (55.3g, 0.40mol) followed by dropwise addition of benzyl bromide (42ml, 0.35mol) over 45 minutes. The mixture was stirred at room temp for 24 hours. Further benzyl bromide (10.0ml, 0.08mol) and potassium carbonate (12.0g, 0.09mol) were added and the mixture heated at reflux for 3 days. On cooling, the mixture was filtered and the filtrate evaporated *in vacuo* to a dark red oil. Trituration with hexane afforded the title compound as an orange crystalline solid (79.0g, 100%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>)  $\delta$ (ppm): 8.05 (d, 1H), 7.91 (s, 1H), 7.25-7.40 (m, 5H), 6.35 (d, 1H), 4.35 (s, 2H), 3.63 (t, 2H), 3.09 (t, 2H). MS: m/z = 255 (MH<sup>+</sup>)

**Description 36****5-Amino-1-benzylindoline (D36)**

A mixture of 1-benzyl-5-nitroindoline (D35, 20.0g, 0.08mol), tin(II)chloride (60.0g, 0.32mol) and conc. HCl (40ml) in methanol (400ml) was heated at reflux for 16h. On cooling, the mixture was evaporated *in vacuo* to a red oil, which was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and water, basified with 40% NaOH solution and the insoluble tin residues removed by filtration. The filtrate was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo* to afford the title compound as a dark green oil (10.5g, 60%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>)  $\delta$ (ppm): 7.23-7.41(m, 5H), 6.58 (s, 1H), 6.45 (dd, 1H), 6.37 (d, 1H), 4.13 (s, 2H), 3.31 (br s, 2H), 3.18 (t, 2H), 2.87 (t, 2H). MS: m/z = 225 (MH<sup>+</sup>)

**Description 37****Diethyl (1-benzylindolin-5-ylamino)methylenemalonate (D37)**

Diethyl ethoxymethylenemalonate (9.45ml, 0.05 mol) was added to a solution of 5-amino-1-benzylindoline (D36, 10.5g, 0.05mol) in toluene (500ml) and the mixture heated at reflux under argon for 1.5 hours. On cooling, the solvent was removed *in vacuo* to give a brown oil (19.6g). Purification by flash chromatography eluting with hexane:EtOAc (70:30) afforded the title compound as a yellow crystalline solid (14.3g, 77%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ(ppm): 8.42 (d, 1H), 7.28-7.38 (m, 5H), 6.93 (s, 1H), 6.83 (dd, 1H), 6.44 (d, 2H), 4.17-4.33 (m, 6H), 3.36 (t, 2H), 2.99 (t, 2H), 1.25-1.40 (m, 6H). MS: m/z = 395 (MH<sup>+</sup>)

**Description 38****Ethyl 1-benzyl-8-chloro-2,3-dihydropyrrolo[2,3-g]quinolin-7-ylcarboxylate (D38)**

Diethyl (1-benzylindolin-5-ylamino)methylenemalonate (D37, 10.0g, 25.3mmol) in phosphorus oxychloride (40ml) was heated at reflux under argon for 2.5 hours. The mixture was concentrated *in vacuo* and the residual oil treated with 10% Na<sub>2</sub>CO<sub>3</sub> solution until basic. Extraction with CH<sub>2</sub>Cl<sub>2</sub> afforded a red gum which was purified using column chromatography eluting with hexane:EtOAc (70:30) to afford the title compound as a yellow crystalline solid (6.3g, 68%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ(ppm): 8.81 (s, 1H), 7.69 (s, 1H), 7.27-7.40 (m, 5H), 7.02 (s, 1H), 4.51 (s, 2H), 4.46 (q, 2H), 3.59 (t, 2H), 3.24 (t, 2H), 1.44 (t, 3H). MS: m/z = 367 (MH<sup>+</sup>)

**Description 39****Ethyl 1-benzyl-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[2,3-g]quinolin-7-ylcarboxylate (D39)**

To a mixture of ethyl 1-benzyl-8-chloro-2,3-dihydropyrrolo[2,3-g]quinolin-7-ylcarboxylate (D38, 5.5g, 15.0mmol) and N-methylpiperazine (5.0ml, 45.0mmol) in DMF (50ml) was added triethylamine (6.3ml, 45.0mmol) and the mixture heated at 90°C under argon for 16 hours. The DMF was removed *in vacuo* and the residue partitioned between CH<sub>2</sub>Cl<sub>2</sub> and water. The organics were separated and the aqueous further extracted with CH<sub>2</sub>Cl<sub>2</sub> (1x). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo* to an orange oil, which was triturated with ethyl acetate (x2) to give the title compound as a yellow solid (4.83g, 75%).

$^1\text{H}$  NMR (250MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm): 8.54 (s, 1H), 7.67 (s, 1H), 7.29-7.41 (m, 5H), 6.76 (s, 1H), 4.45 (s, 2H), 4.41 (q, 2H), 3.60 (t, 2H), 3.17-3.25 (m, 6H), 2.40 (br s, 4H), 2.30 (s, 3H), 1.40 (t, 3H). MS:  $m/z$  = 431 ( $\text{MH}^+$ )

#### Description 40

##### 1-Benzyl-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[2,3-g]quinolin-7-ylcarboxylic acid (D40)

Ethyl 1-benzyl-2,3-dihydro-8-(4-methyl-1-piperazinyl)pyrrolo[2,3-g]quinolin-7-ylcarboxylate (D39, 4.8g, 11.1mmol) in ethanol (100ml) was treated with a solution of sodium hydroxide (0.89g, 22.2mmol) in water (20ml) and the mixture heated at reflux under argon for 16 hours. The ethanol was removed *in vacuo*, the residue diluted with water and treated with 1M HCl solution to pH7. The yellow precipitate was filtered off and dried in a vacuum oven to afford the title compound (4.5g, 100%).

$^1\text{H}$  NMR (250MHz,  $d_6\text{DMSO}$ )  $\delta$ (ppm): 8.35 (s, 1H), 7.56 (s, 1H), 7.39-7.55 (m, 5H), 6.73 (s, 1H), 4.50 (s, 2H), 3.56 (t, 2H), 3.34 (br s, 4H), 3.16 (t, 2H), 2.87 (br s, 4H), 2.61 (s, 3H). Acid proton not observed. MS:  $m/z$  = 403 ( $\text{MH}^+$ )

#### Description 41

##### 1-Benzyl-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[2,3-g]quinoline (D41)

1-Benzyl-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[2,3-g]quinolin-7-ylcarboxylic acid (D40, 4.46g, 11.1mmol) was added in small portions with care down an air condenser to diphenyl ether (100ml) at 250°C over 15 minutes. The mixture was heated at 250-270°C for a further 10 minutes and allowed to cool to 35°C. The solution was then poured into hexane (200ml) and extracted into 2M HCl solution. The acidic extracts were washed with hexane (4x) to remove the diphenyl ether and basified with 10%  $\text{Na}_2\text{CO}_3$  solution. Extraction with ethyl acetate (3x) gave the title compound as a yellow crystalline solid (4.0g, 100%).

$^1\text{H}$  NMR (250MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm): 8.42 (d, 1H), 7.68 (s, 1H), 7.28-7.42 (m, 5H), 6.73 (d, 1H), 6.61 (s, 1H), 4.42 (s, 2H), 3.57 (t, 2H), 3.20 (t, 2H), 3.08 (br s, 4H), 2.42 (br s, 4H), 2.36 (s, 3H). MS:  $m/z$  = 359 ( $\text{MH}^+$ )

#### Description 42

##### 2,3-Dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[2,3-g]quinoline (D42)

1-Benzyl-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[2,3-g]quinoline (D41, 3.98g, 11.1mmol) and conc. HCl (4.0ml) in ethanol (50ml) was hydrogenated over 10% palladium on charcoal at 50psi (344.8KPa) and room temperature for 30 hours. The mixture was

filtered through Celite (Diatomaceous Earth) and basified with solid  $K_2CO_3$ . Evaporation gave an off white solid which was dissolved in  $CH_2Cl_2$  and the inorganics filtered off. Evaporation of the filtrate *in vacuo* afforded the title compound as a yellow solid (1.8g, 74%).

$^1H$  NMR (250MHz,  $CDCl_3$ )  $\delta$ (ppm): 8.46 (d, 1H), 7.72 (s, 1H), 6.96 (s, 1H), 6.77 (d, 1H), 4.14 (br s, 1H), 3.68 (t, 2H), 3.23 (t, 2H), 3.19 (br s, 4H), 2.68 (br s, 4H), 2.41 (s, 3H). MS:  $m/z$  = 269 ( $MH^+$ )

#### Description 43

##### N-[Quinolin-6-yl]acetamide (D43)

To a solution of 6-aminoquinoline (5.0g, 35mmol) in  $CH_2Cl_2$  (200ml) at 0°C was added acetic anhydride (3.5ml, 37mmol) and the mixture stirred whilst warming to room temperature for 16 hours. The mixture was washed with aqueous 10%  $Na_2CO_3$  solution (2x), dried ( $Na_2SO_4$ ) and evaporated *in vacuo* to a white solid (5.7g, 88%).

$^1H$  NMR (250 MHz,  $d_6DMSO$ )  $\delta$  (ppm): 8.78 (m, 1H), 8.38 (d, 1H), 8.28 (d, 1H), 7.97 (d, 1H), 7.78 (dd, 1H), 7.47 (dd, 1H), 3.37 (s, 1H), 2.13 (s, 3H).

#### Description 44

##### N-[1,2,3,4-Tetrahydroquinolin-6-yl]acetamide (D44)

A solution of N-[quinolin-6-yl]acetamide (D43, 5.0g, 26.9mmol) in ethanol was hydrogenated over  $PtO_2$  (0.5g) at 50°C and 50 psi (344.8KPa) for 72 hours. The catalyst was removed by filtering through Celite (Diatomaceous Earth) and the filtrate evaporated *in vacuo* to a pale yellow oil (5.2g, 100%).

$^1H$  NMR (250MHz,  $CDCl_3$ )  $\delta$ (ppm): 7.09 (m, 2H), 6.97 (dd, 1H), 6.41 (d, 1H), 3.27 (t, 2H), 2.99 (br s, 1H), 2.73 (t, 2H), 2.02 (s, 3H), 1.92 (m, 2H).

#### Description 45

##### N-[1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yl]acetamide (D45)

To a stirred solution of N-[1,2,3,4-tetrahydroquinolin-6-yl]acetamide (D44, 5.0g, 26mmol) in acetone (100ml) was added  $K_2CO_3$  (4.4g, 32mmol) followed by dropwise addition of benzyl bromide (3.8ml, 32mmol) over 3 minutes. The mixture was stirred at room temp. for 16 hours and then heated at reflux for 2 hours. On cooling, the mixture was filtered to remove inorganics and the filtrate evaporated to an orange solid (7.7g, 100%).

$^1H$  NMR (250MHz,  $CDCl_3$ )  $\delta$ (ppm): 7.20-7.38 (m, 5H), 7.15 (d, 1H), 6.93 (m, 2H), 6.42 (d, 1H), 4.45 (s, 2H), 3.34 (t, 2H), 2.80 (t, 2H), 2.11 (s, 3H), 1.97 (m, 2H).

**Description 46****6-Amino-1-benzyl-1,2,3,4-tetrahydroquinoline (D46)**

A solution of N-[1-benzyl-1,2,3,4-tetrahydroquinolin-6-yl]acetamide (D45, 6.6g, 23.5mmol) in ethanol (100ml) and 2N NaOH solution (160ml) was heated at reflux for 16 hours. On cooling, the mixture was evaporated *in vacuo* and the residue extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x), the organics dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to a brown oil (5.9g, 100%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ(ppm): 7.20-7.37 (m, 5H), 6.44 (d, 1H), 6.40 (m, 2H), 4.38 (s, 2H), 3.23-3.27 (m, 4H), 2.75 (t, 2H), 1.98 (m, 2H).

**Description 47****Diethyl [1-benzyl-1,2,3,4-tetrahydroquinolin-6-ylamino]methylenemalonate (D47)**

The title compound was prepared from 6-amino-1-benzyl-1,2,3,4-tetrahydroquinoline (D46, 5.6g, 23.5mmol) following a similar procedure to Description 37 (9.18g, 96%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 10.92 (d, 1H), 8.38 (d, 1H), 7.22-7.38 (m, 5H), 6.74-6.81 (m, 2H), 6.45 (d, 1H), 4.48 (s, 2H), 4.16-4.32 (m, 4H), 3.39 (t, 2H), 2.82 (t, 2H), 2.03 (m, 2H), 1.25-1.40 (m, 6H).

**Description 48****Ethyl 1-benzyl-9-chloro-1,2,3,4-tetrahydroquinolin-8-ylcarboxylate (D48)**

The title compound was prepared from diethyl 1-benzyl-1,2,3,4-tetrahydroquinolin-6-ylamino]methylenemalonate (D47, 9.1g, 22.3mmol) following a similar procedure to Description 38 (3.18g, 37%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.79 (s, 1H), 7.68 (s, 1H), 7.28-7.37 (m, 5H), 7.11 (s, 1H), 4.67 (s, 2H), 4.43 (q, 2H), 3.55 (t, 2H), 3.06 (t, 2H), 2.09 (m, 2H), 1.42 (t, 3H).

**Description 49****Ethyl 1-benzyl-9-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydropyrido[2,3-g]quinolin-8-ylcarboxylate (D49)**

The title compound was prepared from ethyl 1-benzyl-9-chloro-1,2,3,4-tetrahydroquinolin-8-ylcarboxylate (D48, 3.1g, 8.14mmol) following a similar procedure to Description 39 (4.2g, 100%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.52 (s, 1H), 7.64 (s, 1H), 7.23-7.36 (m, 5H), 6.78 (s, 1H), 4.67 (s, 2H), 4.38 (q, 2H), 3.57 (t, 2H), 3.08 (m, 6H), 2.18 (s, 3H), 2.07-2.18 (m, 6H), 1.38 (t, 3H).

**Description 50****1-Benzyl-9-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydropyrido[2,3-g]quinolin-8-ylcarboxylic acid (D50)**

The title compound was prepared from ethyl 1-benzyl-9-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydropyrido[2,3-g]quinolin-8-ylcarboxylate (D49, 3.62g, 8.14mmol) following a similar procedure to Description 40 (2.96g, 87%).

<sup>1</sup>H NMR (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 8.33 (s, 1H), 7.52 (s, 1H), 7.21-7.38 (m, 5H), 6.63 (s, 1H), 4.70 (s, 2H), 3.59 (t, 2H), 3.10 (br s, 4H), 3.00 (t, 2H), 2.45 (br s, 4H – partially obscured), 2.39 (s, 3H), 2.04 (m, 2H). Acid proton not observed.

**Description 51****1-Benzyl-9-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydropyrido[2,3-g]quinoline (D51)**

The title compound was prepared from 1-benzyl-9-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydropyrido[2,3-g]quinolin-8-ylcarboxylic acid (D50, 2.5g, 6.0mmol) following a similar procedure to Description 41 (1.7g, 76%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.38 (d, 1H), 7.64 (s, 1H), 7.21-7.36 (m, 5H), 6.63 (d, 1H), 6.58 (s, 1H), 4.64 (s, 2H), 3.58 (t, 2H), 3.05 (t, 2H), 2.91 (br s, 4H), 2.28 (br s, 4H), 2.27 (s, 3H), 2.12 (m, 2H).

**Description 52****9-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydropyrido[2,3-g]quinoline (D52)**

The title compound was prepared from 1-benzyl-9-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydropyrido[2,3-g]quinoline (D51, 1.7g, 4.56mmol) following a similar procedure to Description 42 (1.5g, 100%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.41 (d, 1H), 7.63 (s, 1H), 6.84 (s, 1H), 6.70 (d, 1H), 4.31 (br s, 1H), 3.40 (t, 2H), 3.18 (br s, 4H), 2.99 (t, 2H), 2.67 (br s, 4H), 2.40 (s, 3H), 2.00 (m, 2H).

**Description 53****N-[2-Bromophenyl]glyoxamide oxime (D53)**

A stirred solution of chloral hydrate (26.5g, 0.16mol) in water (350ml) was treated with sodium sulphate (350g, 2.5mol) followed by a solution of 2-bromoaniline (25g, 0.145mol) in a mixture of water (220ml) and conc. HCl acid (13ml). The resulting mixture was treated with a solution of hydroxylamine hydrochloride (31.3g, 0.45mol) in water (140ml) and then

heated up to reflux over 1 hour and held at that temperature for 3 minutes. then cooled in an ice/water bath to room temperature. Brown pellets of the title compound were formed in the mixture. These were filtered off, washed thoroughly with water and dried under vacuum (29.2g, 83%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 8.93 (br s, 1H), 8.41 (dd, 1H), 8.06 (br s, 1H), 7.60 (s, 1H), 7.56 (dd, 1H), 7.34 (dt, 1H), 7.01 (dt, 1H).

#### **Description 54**

##### **7-Bromoisatin (D54)**

Finely ground N-[2-bromophenyl]glyoxamide oxime (D53, 29.2g, 0.12mol) was added portionwise to well stirred conc. H<sub>2</sub>SO<sub>4</sub> (64ml) at 50°C maintaining an internal temperature of 50-70°C during the addition. The mixture was then heated to 80-85°C for 10 minutes, cooled to room temperature and poured onto crushed ice (600g) with stirring. A red/brown precipitate of the title compound formed. This was filtered off, washed with water and dried in a vacuum oven (14.8g, 55%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 7.88 (br s, 1H), 7.71 (dd, 1H), 7.59 (d, 1H), 7.06 (t, 1H).

#### **Description 55**

##### **8-Bromoquinoline-2,4-dicarboxylic acid (D55)**

Potassium hydroxide (31.5g, 0.56mol) was dissolved in water (95ml) with stirring, and the hot solution treated with 7-bromoisatin (D54, 14.8g, 0.065mol) followed by pyruvic acid (7.9ml, 0.12mol). The resulting mixture was stirred at room temperature for 1 hour, then heated at reflux for 1.5 hours. The mixture was allowed to cool, diluted with water (250ml), treated with ethyl acetate (100ml) and stirred vigorously for 10 minutes. The aqueous layer was separated off and added dropwise to cooled, well stirred, conc. HCl acid (25ml). Additional concentrated HCl acid was added to adjust the pH to 1 and the solid was filtered off, washed with water and dried in a vacuum oven to afford the title compound as a tan coloured solid (14.3g, 74%).

<sup>1</sup>H NMR (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 8.79 (dd, 1H), 8.50 (s, 1H), 8.32 (dd, 1H), 7.74 (dd, 1H). Acid protons not discernible.

#### **Description 56**

##### **8-Bromoquinolin-4-ylcarboxylic acid (D56)**

A stirred suspension of 8-bromoquinoline-2,4-dicarboxylic acid (D55, 14.2g, 0.048mol) in nitrobenzene (60ml) was heated under reflux for 2 hours, then cooled to room temperature and treated with hexane (90ml). The precipitate was filtered off, washed with hexane and dried in a vacuum oven to afford the title compound as a grey/brown solid (11.5g, 95%).  
<sup>1</sup>H NMR (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 9.14 (d, 1H), 8.70 (dd, 1H), 8.24 (dd, 1H), 8.00 (d, 1H), 7.63 (dd, 1H). Acid proton not discernible.

#### **Description 57**

##### **8-Bromoquinolin-4-yl isocyanate (D57)**

The title compound was prepared from 8-bromoquinolin-4-ylcarboxylic acid (D56) using a similar procedure to Description 28. The isocyanate was not isolated, but used in the next step as its toluene solution.

#### **Description 58**

##### **8-(2-Fluorophenyl)quinolin-4-ylcarboxylic acid (D58)**

The title compound was prepared from 8-bromoquinolin-4-ylcarboxylic acid (D56) and 2-fluorophenylboronic acid using a similar procedure to Description 3 as a pale brown solid (57%).

<sup>1</sup>H NMR (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 14.07 (br s, 1H), 9.09 (d, 1H), 8.85 (m, 1H), 8.04 (d, 1H), 7.93-7.87 (m, 2H), 7.64-7.55 (m, 2H), 7.44-7.37 (m, 2H).

#### **Description 59**

##### **8-(2-Fluorophenyl)quinolin-4-yl isocyanate (D59)**

The title compound was prepared from 8-(2-fluorophenyl)quinolin-4-ylcarboxylic acid (D58) using a similar procedure to Description 28. The isocyanate was not isolated, but used in the next step as its toluene solution.

#### **Description 60**

##### **8-(2-Methoxyphenyl)quinolin-4-ylcarboxylic acid (D60)**

The title compound was prepared from 8-bromoquinolin-4-ylcarboxylic acid (D56) and 2-methoxyphenylboronic acid using a similar procedure to Description 3 as a pale brown solid (69%).

<sup>1</sup>H NMR (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 13.89 (br s, 1H), 8.92 (d, 1H), 8.65 (dd, 1H), 7.88 (d, 1H), 7.78-7.67 (m, 2H), 7.40 (dt, 1H), 7.22 (dd, 1H), 7.11 (d, 1H), 7.03 (t, 1H), 3.60 (s, 3H).

**Description 61****8-(2-Methoxyphenyl)quinolin-4-yl isocyanate (D61)**

The title compound was prepared from 8-(2-methoxyphenyl)quinolin-4-ylcarboxylic acid (D60) using a similar procedure to Description 28. The isocyanate was not isolated, but used in the next step as its toluene solution.

**Description 62****6-Nitro-4-(piperazin-1-yl)quinoline (D62)**

A solution of 4-chloro-6-nitroquinoline (J. Org. Chem. 1944, 9, 302) (5.0g, 24mmol) and piperazine (8.3g, 96mmol) in toluene (100ml) was heated to reflux for 24 hours under argon. The solution was concentrated *in vacuo* and the residue was dissolved in dichloromethane (150ml), washed with water (3 x 200ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give the title compound as an orange solid (6.0g, 98%). MS: m/z = 259 (MH<sup>+</sup>).

**Description 63****4-(4-*tert*-Butoxycarbonylpiperazin-1-yl)-6-nitroquinoline (D63)**

Water (80ml) was added over 5 min to a stirred solution of 6-nitro-4-(piperazin-1-yl)quinoline (D62, 6.0g, 23.4mmol) in tetrahydrofuran (80ml) at room temperature. To this solution was added a solution of di-*tert*-butyldicarbonate (5.1g, 23.4mmol) in tetrahydrofuran (20ml) over 0.5 hours, followed by the portionwise addition of potassium carbonate (3.4g, 24.6mmol). The mixture was stirred for 3 days and then the organic solvent was evaporated *in vacuo* and the remaining aqueous residue was extracted with dichloromethane (4 x 150ml). The extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to an oil which crystallized in diethyl ether/hexane (1:1) to give the title compound (7.7g, 92%). MS: m/z = 359 (MH<sup>+</sup>).

**Description 64****6-Amino-4-(4-*tert*-butoxycarbonylpiperazin-1-yl)quinoline (D64)**

4-(4-*tert*-Butoxycarbonylpiperazin-1-yl)-6-nitroquinoline (D63, 7.7g, 21.5mmol) was hydrogenated as described in Description 2 to give the title compound as a yellow solid (7.1g, 100%). MS: m/z = 329 (MH<sup>+</sup>).

**Description 65****N-[5-Bromonaphth-1-yl]-N'-[4-(4-*tert*-butoxycarbonylpiperazin-1-yl)quinolin-6-yl]-urea (D65)**

The title compound was prepared from 5-bromonaphth-1-yl isocyanate (D25) and 6-amino-4-(4-*tert*-butoxycarbonylpiperazin-1-yl)quinoline (D64) using a similar procedure to Example 27 (71%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 8.55 (d, 1H), 8.41 (d, 1H), 8.35 (br s, 1H), 7.97 (d, 1H), 7.85 (br s, 1H), 7.73-7.82 (m, 2H), 7.63 (d, 1H), 7.42 (t, 1H), 7.14-7.29 (m, 2H), 7.03 (t, 1H), 6.70 (d, 1H), 3.64 (br m, 4H), 3.09 (br m, 4H), 1.44 (s, 9H). MH<sup>+</sup> 576/578.

### Example 1

#### N-[3-Chloro-4-(pyridin-4-yl)phenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea (E1)

3-Chloro-4-(pyridin-4-yl)aniline (D4, 204mg, 1mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10ml) and triethylamine (101mg, 1mmol) was added to a solution of triphosgene (97mg, 0.33mmol) in CH<sub>2</sub>Cl<sub>2</sub> over a period of 2 minutes and the reaction stirred under argon for 1 hour. The reaction was then treated with 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2, 232mg, 1mmol) and the reaction stirred under argon for 48 hours. The reaction was then washed with saturated aqueous K<sub>2</sub>CO<sub>3</sub> solution, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to a gum. The gum was chromatographed on silica in a gradient of 5-20% MeOH in CH<sub>2</sub>Cl<sub>2</sub>. Elution with 20% MeOH in CH<sub>2</sub>Cl<sub>2</sub> gave the title compound (20mg, 4%), m.p. 151-153°C.

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 9.1 (s, 1H), 8.95 (s, 1H), 8.65 (d, 2H), 8.55 (d, 1H), 8.5 (s, 1H), 7.8 (d, 1H), 7.6 (s, 1H), 7.45 (d, 1H), 7.3 (d, 2H), 7.2 (d, 2H), 6.8 (d, 1H), 3.25 (br s, 4H), 2.65 (br s, 4H), 2.35 (s, 3H).

### Example 2

#### N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[4-(pyridin-4-yl)naphth-1-yl]-urea (E2)

The title compound was prepared from 4-(pyridin-4-yl)-1-naphthylamine (D5) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) following a similar procedure to Example 1 to give the title compound as a yellow powder from ether (38%), m.p. 165 - 170°C.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.95 (s, 1H), 8.7 - 8.5 (m, 4H), 8.25 (s, 1H), 8.0 (d, 1H), 7.9 (d, 1H), 7.8 (d, 1H), 7.7 (d, 1H), 7.3 - 7.1 (m, 6H), 6.75 (d, 1H), 3.2 (br s, 4H), 2.6 (br s, 4H), 2.2 (s, 3H).

### Example 3

#### N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[5-(pyridin-4-yl)naphth-1-yl]-urea (E3)

The title compound was prepared from 5-(pyridin-4-yl)-1-naphthylamine (D6) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) following a similar procedure to Example 1 as needles from ether (33%), m.p. 164 - 166°C.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.8 (s, 1H), 8.65 (d, 2H), 8.55 (m, 2H), 8.15 (s, 1H), 8.0 (d, 1H), 7.8 (t, 2H), 7.5 (d, 1H), 7.35 - 7.2 (m, 5H), 7.1 (d, 1H), 6.7 (d, 1H), 3.2 (br s, 4H), 2.6 (br s, 4H), 2.2 (s, 3H).

#### Example 4

##### N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[quinolin-6-yl]-urea (E4)

The title compound was prepared from 6-aminoquinoline and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) following a similar procedure to Example 1 as a yellow powder from ether (11%), m.p. 240 - 250°C (dec).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD (1:1)) δ (ppm): 8.75 (s, 1H), 8.5 (d, 2H), 8.3 (s, 1H), 8.2 (d, 1H), 8.05 - 7.85 (m, 2H), 7.55 (d, 1H), 7.5 - 7.3 (m, 4H), 6.85 (s, 1H), 3.35 (br s, 4H), 2.85 (br s, 4H), 2.45 (s, 3H).

#### Example 5

##### 4-Bromo-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide (E5)

4-Bromonaphth-1-ylacetic acid (J. Org. Chem. 1951, 16, 1588) (0.58g, 2.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50ml) was treated with oxalyl chloride (830mg, 6.6mmol) at room temperature with continuous stirring for 2 hours. The reaction was then concentrated *in vacuo* and azeotroped with toluene to remove excess oxalyl chloride. The acid chloride was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> and treated with 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2, 0.5g, 2.192 mmol) and triethylamine (224mg, 2.2 mmol) with continuous stirring at room temperature for 18 hours. The reaction was then washed with saturated aqueous potassium carbonate solution, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to a gum (760mg, 70%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.6 (d, 1H), 8.55 (s, 1H), 8.35 (d, 1H), 8.0 (d, 1H), 7.85 - 7.75 (dd, 2H), 7.7 - 7.6 (m, 3H), 7.35 (d, 1H), 7.1 (d, 1H), 6.75 (d, 1H), 4.2 (s, 2H), 3.25 (br s, 4H), 2.7 (br s, 4H), 2.4 (s, 3H).

#### Example 6

##### 5-Bromo-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide (E6).

The title compound was prepared from 5-bromonaphth-1-ylacetic acid (Bull. Soc. Chim. Fr. 1968, 7, 2957) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) following a similar procedure to Example 5 (48%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.6 (d, 1H), 8.5 (s, 1H), 8.3 (d, 1H), 7.85 (s, 1H), 7.8 (d, 1H), 7.65 - 7.5 (m, 2H), 7.45 (s, 1H), 7.4 (d, 1H), 7.35 (d, 1H), 7.1 (dd, 1H), 6.8 (d, 1H), 4.25 (s, 2H), 3.25 (br s, 4H), 2.75 (br s, 4H), 2.4 (s, 3H).

#### Example 7

##### **N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-4-(pyridin-4-yl)naphth-1-ylacetamide (E7)**

The title compound was prepared from 4-bromo-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide (E5) and pyridin-4-ylboronic acid using a similar procedure to Description 3 (56%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.7 (d, 2H), 8.6 (m, 2H), 8.15 (d, 1H), 8.05 (s, 1H), 7.9 (d, 1H), 7.85 (d, 1H), 7.65 - 7.4 (m, 6H), 7.2 (dd, 1H), 6.8 (d, 1H), 4.3 (s, 2H), 3.25 (br s, 4H), 2.7 (br s, 4H), 2.4 (s, 3H).

#### Example 8

##### **N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-5-(pyridin-4-yl)naphth-1-ylacetamide (E8)**

The title compound was prepared from 5-bromo-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide (E6) following a similar procedure to Description 3 as a yellow foam (54%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.75 (d, 2H), 8.6 (d, 2H), 8.15 (d, 1H), 8.05 (s, 1H), 7.85 (dd, 2H), 7.65 - 7.35 (m, 6H), 7.15 (dd, 1H), 6.8 (d, 1H), 4.3 (s, 2H), 3.25 (br s, 4H), 2.7 (br s, 4H), 2.4 (s, 3H).

#### Example 9

##### **N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[4-(pyridin-4-yl)-3-trifluoromethylphenyl]-urea (E9)**

The title compound was prepared from 4-(pyridin-4-yl)-3-trifluoromethylaniline (D8) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) following a similar procedure to Example 1 as a yellow powder (47%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 9.3 (s, 1H), 9.2 (s, 1H), 8.6 (d, 2H), 8.55 (d, 2H), 7.8 (m, 2H), 7.7 (d, 1H), 7.2 (d, 2H), 7.1 (m, 2H), 6.8 (d, 1H), 3.3 (br s, 4H), 2.65 (br s, 4H), 2.35 (s, 3H).

#### Example 10

##### **N-[3-Cyano-4-(pyridin-4-yl)phenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea (E10)**

The title compound was prepared from 3-cyano-4-(pyridin-4-yl)aniline (D10) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) following a similar procedure to Example 1 (35%).  
<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 9.3 (br s, 1H), 9.1 (br s, 1H), 8.7 (d, 2H), 8.6 (d, 1H), 8.5 (s, 1H), 7.9 (s, 1H), 7.85 (d, 1H), 7.45 (d, 2H), 7.35 (d, 1H), 7.2 (d, 1H), 7.1 (s, 1H), 6.85 (m, 1H), 3.25 (m, 4H), 2.7 (m, 4H), 2.4 (s, 3H).

#### Example 11

##### N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[quinolin-5-yl]-urea (E11)

The title compound was prepared from 5-aminoquinoline and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) following a similar procedure to Example 1 as a yellow solid (33%).

<sup>1</sup>H NMR (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 9.4 (s, 1H), 9.05 (s, 1H), 8.95 (d, 1H), 8.6 (d, 1H), 8.55 (d, 1H), 8.3 (d, 1H), 8.05 (dd, 1H), 7.9 (d, 1H), 7.8-7.7 (m, 3H), 7.6 (dd, 1H), 6.9 (d, 1H), 3.2 (m, 4H), 2.65 (m, 4H), 2.3 (s, 3H).

#### Example 12

##### N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[quinolin-8-yl]-urea (E12)

The title compound was prepared from 8-aminoquinoline and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) following a similar procedure to Example 1 (60%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 9.7 (s, 1H), 8.7 (d, 1H), 8.6 (d, 1H), 8.4 (s, 1H), 8.25 (m, 1H), 8.0 (d, 1H), 7.95 (d, 1H), 7.7 (d, 1H), 7.5 (t, 1H), 7.35 (s, 1H), 7.31 (d, 1H), 7.25 (dd, 1H), 7.01 (d, 1H), 3.2 (m, 4H), 2.6 (m, 4H), 2.3 (s, 3H).

#### Example 13

##### N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[quinolin-3-yl]-urea (E13)

The title compound was prepared from 3-aminoquinoline and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) following a similar procedure to Example 1 (8.5%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 9.4 (s, 1H), 9.25 (s, 1H), 8.75 (s, 1H), 8.5 (s, 1H), 8.4 (d, 1H), 7.9 (d, 1H), 7.8 (d, 1H), 7.65 (d, 1H), 7.55-7.45 (m, 4H), 6.7 (d, 1H), 3.25 (m, 4H), 2.6 (m, 4H), 2.3 (s, 3H).

#### Example 14

##### 2,3-Dichloro-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide (E14)

The title compound was prepared from 2,3-dichlorophenylacetic acid (D13) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) following a similar procedure to Example 5 to give a solid, which was crystallised from acetone (76%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.65 (d, 1H), 8.55 (s, 1H), 7.95 (d, 1H), 7.75 (s, 1H), 7.45 (d, 1H), 7.4 (d, 2H), 7.3 (t, 1H), 6.8 (d, 1H), 3.9 (s, 2H), 3.35 (m, 4H), 2.7 (m, 4H), 2.4 (s, 3H).

#### Example 15

##### 5-(4-Acetylphenyl)-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide (E15)

The title compound was prepared from 5-bromo-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide (E6) and 4-acetylphenylboronic acid following a similar procedure to Description 3 (35%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.6 (s, 2H), 8.3 (s, 1H), 8.05 (m, 3H), 7.8 (t, 2H), 7.7-7.35 (m, 6H), 7.25 (m, 1H), 6.8 (d, 1H), 4.25 (s, 2H), 3.25 (br s, 4H), 2.65 (br s, 7H), 2.3 (s, 3H).

#### Example 16

##### N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[quinolin-4-yl]-urea (E16)

The title compound was prepared from 4-aminoquinoline and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) following a similar procedure to Example 1 (6%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 9.85 (s, 1H), 8.75 (d, 1H), 8.55 (s, 1H), 8.4 (m, 1H), 8.35 (d, 1H), 7.95 (d, 2H), 7.8 (d, 1H), 7.5 (m, 2H), 7.1 (m, 1H), 6.75 (d, 1H), 6.05 (s, 1H), 3.25 (br s, 4H), 2.65 (br s, 4H), 2.3 (s, 3H).

#### Example 17

##### N-[3-Chloro-4-(pyridin-4-yl)phenyl]-N'-[4-(1-methylpiperidin-4-yl)quinolin-6-yl]-urea (E17)

The title compound was prepared from 3-chloro-4-(pyridin-4-yl)aniline (D4) and 6-amino-4-(1-methylpiperidin-4-yl)quinoline (D16) following a similar procedure to Example 1. The crude product was purified by chromatography on silica gel eluting with a gradient of 50-70% methanol in dichloromethane. The main slow running fraction was collected to give the title compound as a colourless powder (7%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.9 (s, 1H), 8.8 (s, 1H), 8.7 (d, 1H), 8.6 (m, 3H), 7.9 (d, 1H), 7.6 (d, 1H), 7.4 (dd, 1H), 7.3 (d, 2H), 7.25 (d, 2H), 7.15 (d, 1H), 3.3-2.95 (m, 3H), 3.0 (s, 3H), 2.3-2.1 (m, 2H), 2.0-1.8 (m, 4H). MH<sup>+</sup> 472.

#### Example 18

**N-[3-Methyl-4-(6-methylpyridin-2-yl)phenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea (E18)**

The title compound was prepared from 3-methyl-4-(6-methylpyridin-2-yl)aniline (D18) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using a similar procedure to Example 1 (24%).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>DMSO) δ (ppm): 9.03 (s, 1H), 8.78 (s, 1H), 8.50 (d, 1H), 8.17 (d, 1H), 7.84 (d, 1H), 7.74-7.64 (m, 2H), 7.47-7.20 (m, 4H), 7.14 (d, 1H), 6.88 (d, 1H), 3.14 (br s, 4H), 2.60 (br s, 4H), 2.47 (s, 3H), 2.31 (s, 3H), 2.27 (s, 3H).

**Example 19****N-[4-(2,6-Dimethylpyridin-4-yl)-3-methylphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea (E19)**

The title compound was prepared from 4-(2,6-dimethylpyridin-4-yl)-3-methylaniline (D19) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using a similar procedure to Example 1 (55%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 8.99 (br s, 1H), 8.57 (d, 1H), 8.53 (s, 2H), 7.81 (d, 1H), 7.32-7.24 (m, 2H), 7.11 (dd, 1H), 7.05 (d, 1H), 6.78 (br s, 3H), 3.24 (br s, 4H), 2.63 (br s, 4H), 2.51 (s, 6H), 2.30 (s, 3H), 2.13 (s, 3H).

**Example 20****N-[5-Cyanonaphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea (E20)**

The title compound was prepared from 5-cyano-1-naphthylamine (EP 456090) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using a similar procedure to Example 1 as a pale buff solid (50%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 8.70 (s, 1H), 8.55 (d, 1H), 8.50 (d, 1H), 8.11 (s, 1H), 8.04 (d, 1H), 7.93 (d, 1H), 7.83 (q, 1H), 7.72 (d, 1H), 7.50 (t, 1H), 7.19 (t, 1H), 7.12 (dd, 2H), 6.77 (d, 1H), 3.22 (s, 4H), 2.60 (s, 4H), 2.26 (s, 3H).

**Example 21****N-[5-(5-Methyl-1,2,4-oxadiazol-3-yl)naphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea (E21)**

The title compound was prepared from 5-(5-methyl-1,2,4-oxadiazol-3-yl)-1-naphthylamine (D22) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using a similar procedure to Example 1. The hydrochloride salt was isolated as a green powder (34%).

<sup>1</sup>H NMR (HCl salt) (250MHz, d<sup>6</sup>DMSO) δ (ppm): 11.36 (s, 1H), 11.05 (s, 1H), 9.80 (s, 1H), 8.76 (d, 1H), 8.68 (d, 1H), 8.59 (s, 1H), 8.18 (q, 3H), 7.96 (d, 1H), 7.76-7.64 (m, 2H), 7.33 (d, 1H), 4.22 (br s, 2H), 3.62 (br s, 4H), 2.90 (s, 3H), 2.75 (s, 3H). 2H obscured by H<sub>2</sub>O signal.

#### Example 22

##### **N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[5-(pyrimidin-2-yloxy)naphth-1-yl]-urea (E22)**

The title compound was prepared from 5-(pyrimidin-2-yloxy)-1-naphthylamine (D23) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using a similar procedure to Example 1 as a pale yellow solid (10%).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>DMSO) δ (ppm): 9.41 (s, 1H), 8.91 (s, 1H), 8.63 (d, 2H), 8.54 (d, 1H), 8.32 (d, 1H), 8.08 (d, 1H), 7.93 (dd, 1H), 7.88 (d, 1H), 7.76-7.63 (m, 2H), 7.50 (m, 2H), 7.41 (d, 1H), 7.28 (t, 1H), 6.92 (d, 1H), 3.15 (br s, 4H), 2.64 (br s, 4H), 2.30 (s, 3H).

#### Example 23

##### **N-[5-Acetylnaphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea (E23)**

The title compound was prepared from 5-acetyl-1-naphthylamine (D24) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using a similar procedure to Example 1. The hydrochloride salt was isolated as a yellow/green solid (72%).

<sup>1</sup>H NMR (HCl salt) (250MHz, d<sup>6</sup>DMSO) δ (ppm): 10.77 (s, 1H), 9.62 (s, 1H), 8.70 (d, 1H), 8.63 (d, 1H), 8.53 (d, 1H), 8.27 (d, 1H), 8.10 (m, 4H), 7.87 (dd, 1H), 7.69-7.57 (m, 2H), 7.23 (d, 1H), 3.50 (br s, 4H), 3.37 (br s, 4H), 2.89 (s, 3H), 2.74 (s, 3H).

#### Example 24

##### **N-[5-Bromonaphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea (E24)**

The title compound was prepared from 5-bromonaphth-1-yl isocyanate (D25) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using a similar procedure to that described for Example 27. The free base was converted to monohydrochloride salt as a yellow solid from acetone.

<sup>1</sup>H NMR (HCl salt) (250MHz, d<sup>6</sup>DMSO) δ (ppm): 11.19 (br s, 1H), 11.03 (s, 1H), 9.76 (s, 1H), 8.90 (d, 1H), 8.69 (s, 1H), 8.59 (d, 1H), 8.28-8.23 (m, 2H), 8.07-8.03 (m, 3H), 7.80 (t, 1H), 7.61 (t, 1H), 7.46 (d, 1H), 4.36 (br d, 2H), 3.82-3.72 (br m, 6H), 3.10 (s, 3H).

#### Example 25

**N-[5-(6-Methylpyridin-2-yl)naphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea (E25)**

The title compound was prepared from 5-(6-methylpyridin-2-yl)naphth-1-yl isocyanate (D28) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using a similar procedure to Example 27 (24%).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>DMSO) δ (ppm): 9.47 (s, 1H), 8.96 (s, 1H), 8.55 (d, 1H), 8.34 (d, 1H), 8.27 (d, 1H), 8.01 (d, 1H), 7.95-7.82 (m, 2H), 7.78-7.64 (m, 3H), 7.60 (d, 1H), 7.55-7.40 (m, 2H), 7.34 (d, 1H), 6.93 (d, 1H), 3.18 (br s, 4H), 2.64 (br s, 4H), 2.57 (s, 3H), 2.30 (s, 3H).

**Example 26****N-[5-(2-Methylpyridin-5-yl)naphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea (E26)**

The title compound was prepared from 5-(2-methylpyridin-5-yl)naphth-1-yl isocyanate (D30) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using a similar procedure to Example 27 (45%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 8.96 (s, 1H), 8.58-8.51 (m, 2H), 8.46 (d, 1H), 8.28 (s, 1H), 7.92 (d, 1H), 7.80-7.70 (m, 2H), 7.52-7.43 (m, 2H), 7.30-7.00 (m, 5H), 6.70 (d, 1H), 3.15 (br s, 4H), 2.62 (s, 3H), 2.14 (s, 3H).

**Example 27****N-[5-(2-Methylpyridin-3-yl)naphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea (E27)**

A solution of 5-(2-methylpyridin-3-yl)naphth-1-yl isocyanate (D32, 1.2 mmol) in toluene (13ml) was added to a stirred solution of 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2, 210mg, 0.83 mmol) and maintained at room temperature for 48 hours. The mixture was concentrated *in vacuo* and the residue purified by column chromatography on basic alumina eluting with 0-10% methanol/ethyl acetate to afford the title compound as a pale yellow foam (370mg, 87%). This was converted to its hydrochloride salt as a pale yellow solid from acetone.

<sup>1</sup>H NMR (free base) (250MHz, CDCl<sub>3</sub>) δ (ppm): 8.64-8.55 (m, 3H), 8.35 (br s, 1H), 8.05 (d, 1H), 7.88 (d, 1H), 7.83-7.78 (m, 2H), 7.43 (dd, 1H), 7.38-7.30 (m, 2H), 7.28-7.12 (m, 4H), 6.79 (d, 1H), 3.24 (br s, 4H), 2.64 (br s, 4H), 2.26 (s, 3H), 2.19 (s, 3H).

**Example 28**

**N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[5-(pyrimidin-2-yl)naphth-1-yl]-urea (E28)**

The title compound was prepared from 5-(pyrimidin-2-yl)naphth-1-yl isocyanate (D34) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using a similar procedure to that described for Example 27. The free base was converted to monohydrochloride salt, as a yellow solid.

<sup>1</sup>H NMR (HCl salt) (250MHz, d<sup>6</sup>DMSO) δ (ppm): 15.3 (br, 1H), 11.35 (br, 1H), 11.05 (s, 1H), 9.59 (s, 1H), 8.78 (d, 1H), 8.61 (s, 1H), 8.47 (d, 1H), 8.17 (d, 1H), 8.08 (d, 1H), 7.98 (m, 3H), 7.68 (d, 1H), 7.51-7.62 (m, 3H), 7.34 (d, 1H), 4.23 (br, 2H), 3.76 (br, 2H), 3.62 (br, 2H), 3.39 (obscured by water peak, 2H), 2.89 (s, 3H).

**Example 29****N-[5-Bromonaphth-1-yl]-N'-[4-(piperazin-1-yl)quinolin-6-yl]-urea (E29)**

N-[5-Bromonaphth-1-yl]-N'-[4-(4-*tert*-butoxycarbonylpiperazin-1-yl)quinolin-6-yl]-urea (D65, 200mg, 0.35mmol) in THF (30ml) was treated with conc. HCl (1ml) and heated at reflux for 1.5 hours. A cream coloured precipitate was filtered off to give the hydrochloride salt of the title compound (27mg, 16%).

<sup>1</sup>H NMR (HCl salt) (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 11.17 (s, 1H), 9.80 (s, 1H), 9.58 (br m, 2H), 8.75 (d, 1H), 8.56 (m, 2H), 8.17 (m, 2H), 7.90-8.01 (m, 3H), 7.68 (t, 1H), 7.52 (t, 1H), 7.32 (d, 1H), 3.92 (br m, 4H), 3.44 (br m, 4H, partially obscured). MH<sup>+</sup> 476/478.

**Example 30****2,3-Dihydro-8-(4-methylpiperazin-1-yl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]pyrrolo[2,3-g]quinoline (E30)**

The title compound was prepared from 4-(pyridin-4-yl)-1-naphthylamine (D5) and 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[2,3-g]quinoline (D42) using a similar procedure to Example 1 as the hydrochloride salt, a yellow solid (67%).

<sup>1</sup>H NMR (HCl salt) (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 11.74 (br s, 1H), 9.41 (s, 1H), 8.98 (d, 2H), 8.73 (d, 1H), 8.41 (s, 1H), 8.24 (d, 1H), 8.13 (s, 1H), 8.05 (d, 2H), 7.89 (d, 1H), 7.60-7.75 (m, 4H), 7.34 (d, 1H), 4.55 (t, 2H), 4.10 (br d, 2H), 3.50-3.70 (m, 6H), 3.30 (m, 2H), 2.78 (d, 3H). MS: m/z = 515 (MH<sup>+</sup>)

**Example 31****2,3-Dihydro-8-(4-methylpiperazin-1-yl)-1-[5-(5-methyl-1,2,4-oxadiazol-3-yl)naphth-1-ylaminocarbonyl]pyrrolo[2,3-g]quinoline (E31)**

The title compound was prepared from 5-(5-methyl-1,2,4-oxadiazol-3-yl)-1-naphthylamine (D22) and 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[2,3-g]quinoline (D42) using a similar procedure to Example 1 as the hydrochloride salt, a yellow solid (83%).

<sup>1</sup>H NMR (HCl salt) (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 11.46 (br s, 1H), 9.30 (s, 1H), 8.71 (m, 2H), 8.39 (s, 1H), 8.34 (d, 1H), 8.21 (d, 1H), 8.07 (s, 1H), 7.64-7.77 (m, 3H), 7.30 (d, 1H), 4.51 (t, 2H), 4.01 (br m, 2H), 3.58 (t, 2H), 3.20-3.40 (br m, 6H), 2.77 (s, 3H), 2.76 (s, 3H). MS: m/z = 520 (MH<sup>+</sup>)

#### Example 32

##### 2,3-Dihydro-8-(4-methylpiperazin-1-yl)-1-[5-(pyrimidin-2-yloxy)naphth-1-ylaminocarbonyl]pyrrolo[2,3-g]quinoline (E32)

The title compound was prepared from 5-(pyrimidin-2-yloxy)-1-naphthylamine (D23) and 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[2,3-g]quinoline (D42) using a similar procedure to Example 1 as the hydrochloride salt, a yellow solid (47%).

<sup>1</sup>H NMR (HCl salt) (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 11.59 (br s, 1H), 9.27 (s, 1H), 8.73 (d, 1H), 8.65 (d, 2H), 8.40 (s, 1H), 8.12 (s, 1H), 8.01 (d, 1H), 7.71 (m, 1H), 7.51-7.63 (m, 3H), 7.42 (d, 1H), 7.29-7.34 (m, 2H), 4.51 (t, 2H), 4.07 (br d, 2H), 3.51-3.68 (m, 6H), 3.31 (m, 2H), 2.78 (d, 3H). MS: m/z = 532 (MH<sup>+</sup>)

#### Example 33

##### 9-(4-Methylpiperazin-1-yl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1,2,3,4-tetrahydropyrido[2,3-g]quinoline (E33)

The title compound was prepared from 4-(pyridin-4-yl)-1-naphthylamine (D5) and 9-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydropyrido[2,3-g]quinoline (D52) using a similar procedure to Example 1 as the hydrochloride salt, an orange solid (59%).

<sup>1</sup>H NMR (HCl salt) (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 11.57 (br s, 1H), 9.50 (s, 1H), 8.88 (d, 2H), 8.73 (d, 1H), 8.36 (s, 1H), 8.22 (d, 1H), 7.98 (s, 1H), 7.86 (m, 3H), 7.74 (d, 1H), 7.57-7.71 (m, 3H), 7.25 (d, 1H), 4.18 (m, 2H), 4.09 (t, 2H), 3.20-3.80 (br m, 6H), 3.08 (t, 2H), 2.73 (s, 3H), 2.11 (m, 2H). MS: m/z = 529 (MH<sup>+</sup>)

#### Example 34

##### 9-(4-Methylpiperazin-1-yl)-1-[5-(pyrimidin-2-yloxy)naphth-1-ylaminocarbonyl]-1,2,3,4-tetrahydropyrido[2,3-g]quinoline (E34)

The title compound was prepared from 5-(pyrimidin-2-yloxy)-1-naphthylamine (D23) and 9-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydropyrido[2,3-g]quinoline (D52) using a similar procedure to Example 1 as the hydrochloride salt, a yellow solid (64%).

<sup>1</sup>H NMR (HCl salt) (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 11.44 (br s, 1H), 9.39 (s, 1H), 8.73 (d, 1H), 8.66 (d, 2H), 8.38 (s, 1H), 8.00 (m, 2H), 7.49-7.69 (m, 4H), 7.41 (d, 1H), 7.24-7.32 (m, 2H), 4.05-4.23 (m, 6H), 3.68 (t, 2H), 3.20-3.40 (m, 2H), 3.08 (t, 2H), 2.74 (d, 3H), 2.11 (t, 2H). MS: m/z = 546 (MH<sup>+</sup>)

#### Example 35

##### N-[8-Bromoquinolin-4-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea (E35)

The title compound was prepared from 8-bromoquinolin-4-yl isocyanate (D57) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using a similar procedure to that described for Example 27 as a cream coloured solid (3%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 9.88 (br s, 1H), 9.25 (br s, 1H), 8.91 (d, 1H), 8.65-8.61 (m, 2H), 8.47 (d, 1H), 7.93 (d, 1H), 7.80 (d, 1H), 7.65 (d, 1H), 7.01-6.95 (m, 2H), 6.85 (d, 1H), 3.34 (br s, 4H), 2.70 (br s, 4H), 2.40 (s, 3H).

#### Example 36

##### N-[8-(2-Fluorophenyl)quinolin-4-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea (E36)

The title compound was prepared from 8-(2-fluorophenyl)quinolin-4-yl isocyanate (D59) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using a similar procedure to Example 27 as a yellow solid (91%). This was converted to its hydrochloride salt as a yellow solid from acetone.

<sup>1</sup>H NMR (HCl salt) (250MHz, d<sup>6</sup>DMSO) δ (ppm): 12.19 (s, 1H), 11.72 (br s, 1H), 11.32 (br s, 1H), 9.29 (d, 1H), 8.87-8.74 (m, 3H), 8.59 (s, 1H), 8.23 (d, 1H), 8.06-7.92 (m, 3H), 7.67-7.56 (m, 2H), 7.48-7.39 (m, 3H), 4.33 (br d, 2H), 3.88 (br t, 2H), 3.55 (br, 4H), 2.91 (s, 3H).

#### Example 37

##### N-[8-(2-Methoxyphenyl)quinolin-4-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea (E37)

The title compound was prepared from 8-(2-methoxyphenyl)quinolin-4-yl isocyanate (D61) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using a similar procedure to Example 27 as a yellow solid (8%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 9.67 (br s, 1H), 8.85-8.75 (m, 2H), 8.66 (d, 1H), 8.59 (d, 1H), 8.39 (d, 1H), 7.85 (d, 1H), 7.55-7.51 (m, 2H), 7.24-7.04 (m, 4H), 6.87-6.79 (m, 3H), 3.43 (s, 3H), 3.32 (br s, 4H), 2.70 (br s, 4H), 2.38 (s, 3H).

### Examples 38 - 56

The following compounds were prepared by a similar procedure to that described for Example 27 using the appropriate isocyanate together with 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2)

Eg. no.	Compound	MH+
38	N-[2-Biphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	438.3
39	N-[2,3-Dichlorophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	430.2/ 432.2
40	N'-[4-Biphenyl]-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	438.3
41	N-[3,4-Dichlorophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	430.2/ 432.2
42	N-[4-Chlorophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	396.3/ 398.3
43	N-[3-Cyanophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	387.3
44	N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[4-phenoxyphenyl]-urea	454.3
45	N-[4-Bromophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	440.2/ 442.2
46	N-[4-Acetylphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	404.3
47	N-[2-Bromophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	440.0/ 442.0
48	N-[3,5-Bis(trifluoromethyl)phenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	498.1
49	N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[naphth-2-yl]-urea	412.2

50	N-[3-Acetylphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	404.2
51	N-[2,6-Difluorophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	398.2
52	N-[3-Bromophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	439.7/ 441.9
53	N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[naphth-1-yl]-urea	412.2
54	N-[2,6-Dichlorophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	430.1/ 432.1
55	N-[4-Chloro-2-methylphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	410.2/ 412.2
56	N-[4-Bromo-3-methylphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea	456.1

**Examples 57 - 68**

The following compounds were prepared from the appropriate carboxylic acid and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide as coupling reagent.

Eg no.	compound	MH+
57	N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-2-nitrophenylacetamide	406.2
58	4-Bromo-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide	441.0/ 442.2
59	N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-4-biphenylacetamide	437.2
60	3,4-Dichloro-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]benzamide	415.1/ 417.1
61	N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]naphth-2-ylacetamide	411.2
62	4-Dimethylamino-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide	404.2

63	3,4-Difluoro-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide	397.2
64	N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-3-phenoxyphenylacetamide	453.2
65	N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylcarboxamide	397.2
66	N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-4-phenoxybenzamide	439.2

**Example 67**

**N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl]-urea (E67)**

The title compound was prepared from 6-amino-3,4-dihydro-1(2H)-naphthalenone and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using a similar procedure to Example 1 as a yellow foam (47%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 9.2 (s, 1H), 8.95 (s, 1H), 8.6 (d, 1H), 8.5 (s, 1H), 7.9 (d, 1H), 7.8 (d, 1H), 7.6 (s, 1H), 7.2 (d, 1H), 7.05 (d, 1H), 6.8 (d, 1H), 3.25 (br s, 4H), 2.85 (m, 2H), 2.6 (m, 6H), 2.3 (s, 3H), 2.05 (m, 2H).

**Example 68**

**N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[5-oxoindan-2-yl]-urea (E68)**

The title compound was prepared from 5-amino-1-indanone and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D2) using a similar procedure to Example 1 as a yellow foam (20%).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.8 (br s, 2H), 8.65 (d, 1H), 8.45 (d, 1H), 7.95 (s, 1H), 7.85 (d, 1H), 7.6 (d, 1H), 7.25 (dd, 1H), 7.05 (d, 1H), 6.85 (d, 1H), 3.3 (br s, 4H), 3.1 (m, 2H), 2.7 (m, 6H), 2.4 (s, 3H).

**Example 69**

**2,3-Dihydro-8-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]pyrrolo[2,3-g]quinoline (E69)**

The title compound was prepared from 6-amino-3,4-dihydro-1(2H)-naphthalenone and 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[2,3-g]quinoline (D42) using a similar procedure to Example 1 as the hydrochloride salt, a yellow solid (55%).

<sup>1</sup>H NMR (HCl salt) (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 11.74 (br s, 1H), 9.29 (s, 1H), 8.73 (d, 1H), 8.42 (s, 1H), 8.07 (s, 1H), 7.85 (d, 1H), 7.66 (m, 2H), 7.36 (d, 1H), 4.39 (t, 2H), 4.16 (t, 2H), 3.79 (t, 2H), 3.25-3.62 (m, 6H), 2.93 (t, 2H), 2.88 (d, 3H), 2.57 (t, 2H), 2.04 (m, 2H). MH<sup>+</sup> 456.

#### Example 70

##### 9-(4-Methylpiperazin-1-yl)-1-[(5-oxo-5,6,7,8-tetrahydronaphth-6-yl)aminocarbonyl]-1,2,3,4-tetrahydropyrido[2,3-g]quinoline (E70)

The title compound was prepared from 6-amino-3,4-dihydro-1(2H)-naphthalenone and 9-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydropyrido[2,3-g]quinoline (D52) using a similar procedure to Example 1 as the hydrochloride salt, a dark yellow solid (71%).

<sup>1</sup>H NMR (HCl salt) (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 11.59 (br s, 1H), 9.69 (s, 1H), 8.75 (d, 1H), 8.13 (s, 1H), 8.00 (s, 1H), 7.83 (d, 1H), 7.52 (m, 2H), 7.27 (d, 1H), 4.13-4.18 (m, 2H), 3.87 (t, 2H), 3.64 (br m, 2H), 3.27 (m, 4H), 3.01 (t, 2H), 2.91 (t, 2H), 2.71 (s, 3H), 2.56 (t, 2H), 2.01 (m, 4H). MH<sup>+</sup> 470.

#### Pharmacological Data

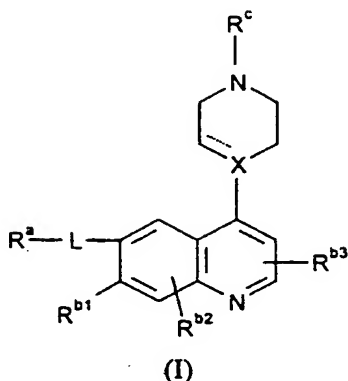
The affinities of the compounds of this invention were determined by methods described above.

##### 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> Receptor Binding

Examples 1-5, 7, 9, 10, 13, 14, 18-21, 25-27, 30, 35-37, 39, 40, 44, 46, 58, 60 and 66-68 had pK<sub>i</sub> values > 8.5 at 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors

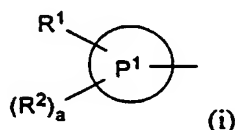
## CLAIMS

1. A compound of formula (I) or a salt thereof:



in which  $R^a$  is selected from a group of formula (i), (ii) or (iii);

Group of formula (i)



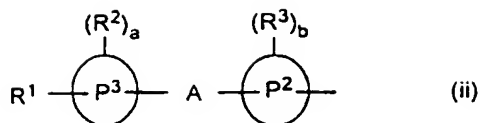
in which  $P^1$  is phenyl, bicyclic aryl, a 5 to 7 membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur;

$R^1$  is hydrogen, halogen,  $C_{1-6}$ alkyl,  $C_{3-6}$ cycloalkyl,  $C_{1-6}$ alkoxy, hydroxy, hydroxy $C_{1-6}$ alkyl, hydroxy $C_{1-6}$ alkoxy,  $C_{1-6}$ alkoxy $C_{1-6}$ alkoxy,  $C_{1-6}$ alkanoyl, nitro, trifluoromethyl, cyano,  $SR^9$ ,  $SOR^9$ ,  $SO_2R^9$ ,  $SO_2NR^{10}R^{11}$ ,  $CO_2R^{10}$ ,  $CONR^{10}R^{11}$ ,  $CONR^{10}(CH_2)_cCO_2R^{11}$ ,  $(CH_2)_cNR^{10}R^{11}$ ,  $(CH_2)_cCONR^{10}R^{11}$ ,  $(CH_2)_cNR^{10}COR^{11}$ ,  $(CH_2)_cCO_2C_{1-6}$ alkyl,  $CO_2(CH_2)_cOR^{10}$ ,  $NR^{10}R^{11}$ ,  $NR^{10}CO_2R^{11}$ ,  $NR^{10}CONR^{10}R^{11}$ ,  $CR^{10}=NOR^{11}$ ,  $CNR^{10}=NOR^{11}$ , where  $R^9$ ,  $R^{10}$  and  $R^{11}$  are independently hydrogen or  $C_{1-6}$ alkyl and c is 1 to 4;

a is 0, 1 or 2; and

$R^2$  is halogen,  $C_{1-6}$ alkyl,  $C_{3-6}$ cycloalkyl,  $C_{3-6}$ cycloalkenyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkanoyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano,  $CO_2R^{10}$ ,  $CONR^{10}R^{11}$ ,  $NR^{10}R^{11}$  where  $R^{10}$  and  $R^{11}$  are as defined above;

Group of formula (ii)



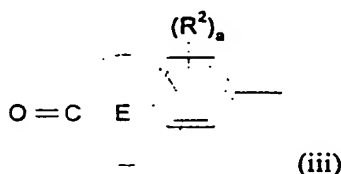
wherein P<sup>2</sup> and P<sup>3</sup> are independently phenyl, bicyclic aryl, a 5- to 7- membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic heterocyclic group containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur; A is a bond or oxygen, S(O)<sub>m</sub> where m is 0 to 2, carbonyl, CH<sub>2</sub> or NR<sup>4</sup> where R<sup>4</sup> is hydrogen or C<sub>1-6</sub>alkyl;

R<sup>1</sup> is as defined above for formula (i) or is a 5 to 7-membered heterocyclic ring, containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur, optionally substituted by C<sub>1-6</sub>alkyl, halogen or C<sub>1-6</sub>alkanoyl;

a and b are independently 0, 1 or 2; and

R<sup>2</sup> and R<sup>3</sup> are independently halogen, C<sub>1-6</sub>alkyl, C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub>cycloalkenyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkanoyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO<sub>2</sub>R<sup>10</sup>, CONR<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>R<sup>11</sup> where R<sup>10</sup> and R<sup>11</sup> are as defined above;

#### Group of formula (iii)

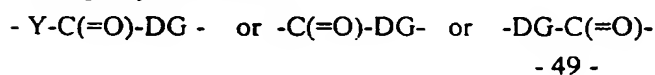


in which the ring E is a 5, 6 or 7 -membered carbocyclic ring optionally substituted by one or more C<sub>1-6</sub>alkyl groups, fused at the 2,3- or 3,4-positions of the adjacent phenyl ring, the ring E being optionally fused to a further phenyl ring optionally substituted by one or more substituents independently selected from C<sub>1-6</sub>alkyl and halo;

a is 0, 1 or 2; and

R<sup>2</sup> is halogen, C<sub>1-6</sub>alkyl, C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub>cycloalkenyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkanoyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO<sub>2</sub>R<sup>10</sup>, CONR<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>R<sup>11</sup> where R<sup>10</sup> and R<sup>11</sup> are as defined above;

L is a group of formula



in which Y is -NH-, NR<sup>5</sup> where R<sup>5</sup> is C<sub>1-6</sub>alkyl, or Y is -CH<sub>2</sub>- or -O-;  
D is nitrogen, carbon or a CH group, G is hydrogen or C<sub>1-6</sub>alkyl providing that D is nitrogen or a CH group, or G together with R<sup>b1</sup> forms a group W where W is (CR<sup>16</sup>R<sup>17</sup>)<sub>t</sub> where t is 2, 3 or 4 and R<sup>16</sup> and R<sup>17</sup> are independently hydrogen or C<sub>1-6</sub>alkyl or W is (CR<sup>16</sup>R<sup>17</sup>)<sub>u</sub>-J where u is 0, 1, 2 or 3 and J is oxygen, sulphur, CR<sup>16</sup>=CR<sup>17</sup>, CR<sup>16</sup>=N, =CR<sup>16</sup>O, =CR<sup>16</sup>S or =CR<sup>16</sup>-NR<sup>17</sup> provided that u is not 0 when J is oxygen or sulphur;

X is nitrogen or carbon;

R<sup>b1</sup>, R<sup>b2</sup> and R<sup>b3</sup> are independently hydrogen, halogen, hydroxy, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>3-6</sub>cycloalkyl, trifluoromethyl, C<sub>1-6</sub>alkoxy or aryl, or R<sup>b1</sup> together with G forms a group W as defined above;

R<sup>c</sup> is hydrogen or C<sub>1-6</sub>alkyl; and

       is a single bond when X is nitrogen or a single or double bond when X is carbon.

2. A compound according to claim 1 in which P<sup>1</sup> is a phenyl, naphthyl or a quinoline group.
3. A compound according to claim 1 or 2 in which R<sup>1</sup> is halogen or a C<sub>1-6</sub>alkyl.
4. A compound according to any of the preceding claims in which the group L is a group of formula:-  

$$-Y-C(=O)-(DG)-$$
in which Y, D and G are as defined in formula (I).
5. A compound according to any of the preceding claims in which Y is -NH-.
6. A compound according to any of the preceding claims in which D is nitrogen and G is hydrogen.
7. A compound according to any of the preceding claims in which R<sup>b1</sup>, R<sup>b2</sup> and R<sup>b3</sup> are independently hydrogen, halogen or C<sub>1-6</sub>alkoxy.
8. A compound according to any of the preceding claims in which X is nitrogen.
9. A compound according to claim 1 which is:

N-[3-Chloro-4-(pyridin-4-yl)phenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[4-(pyridin-4-yl)naphth-1-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[5-(pyridin-4-yl)naphth-1-yl]-urea  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[quinolin-6-yl]-urea,  
4-Bromo-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide,  
5-Bromo-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide.  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-4-(pyridin-4-yl)naphth-1-ylacetamide,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-5-(pyridin-4-yl)naphth-1-ylacetamide,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[4-(pyridin-4-yl)-3-trifluoromethylphenyl]-  
urea,  
N-[3-Cyano-4-(pyridin-4-yl)phenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[quinolin-5-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[quinolin-8-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[quinolin-3-yl]-urea,  
2,3-Dichloro-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide,  
5-(4-Acetylphenyl)-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[quinolin-4-yl]-urea,  
N-[3-Chloro-4-(pyridin-4-yl)phenyl]-N'-[4-(1-methylpiperidin-4-yl)quinolin-6-yl]-urea,  
N-[3-Methyl-4-(6-methylpyridin-2-yl)phenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-  
urea,  
N-[4-(2,6-Dimethylpyridin-4-yl)-3-methylphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-  
yl]-urea,  
N-[5-Cyanonaphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[5-(5-Methyl-1,2,4-oxadiazol-3-yl)naphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-  
yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[5-(pyrimidin-2-yloxy)naphth-1-yl]-urea,  
N-[5-Acetylnaphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[5-Bromonaphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[5-(6-Methylpyridin-2-yl)naphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[5-(2-Methylpyridin-5-yl)naphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[5-(2-Methylpyridin-3-yl)naphth-1-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[5-(pyrimidin-2-yl)naphth-1-yl]-urea,  
N-[5-Bromonaphth-1-yl]-N'-[4-(piperazin-1-yl)quinolin-6-yl]-urea.  
2,3-Dihydro-8-(4-methylpiperazin-1-yl)-1-[4-(pyridin-4-yl)naphth-1-  
ylaminocarbonyl]pyrrolo[2,3-g]quinoline,

2,3-Dihydro-8-(4-methylpiperazin-1-yl)-1-[5-(5-methyl-1,2,4-oxadiazol-3-yl)naphth-1-ylaminocarbonyl]pyrrolo[2,3-g]quinoline,  
2,3-Dihydro-8-(4-methylpiperazin-1-yl)-1-[5-(pyrimidin-2-yloxy)naphth-1-ylaminocarbonyl]pyrrolo[2,3-g]quinoline,  
9-(4-Methylpiperazin-1-yl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1,2,3,4-tetrahydropyrido[2,3-g]quinoline,  
9-(4-Methylpiperazin-1-yl)-1-[5-(pyrimidin-2-yloxy)naphth-1-ylaminocarbonyl]-1,2,3,4-tetrahydropyrido[2,3-g]quinoline,  
N-[8-Bromoquinolin-4-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[8-(2-Fluorophenyl)quinolin-4-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[8-(2-Methoxyphenyl)quinolin-4-yl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[2-Biphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[2,3-Dichlorophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N'-[4-Biphenyl]-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[3,4-Dichlorophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-Chlorophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[3-Cyanophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[4-phenoxyphenyl]-urea,  
N-[4-Bromophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-Acetylphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[2-Bromophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[3,5-Bis(trifluoromethyl)phenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[3-Acetylphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[2,6-Difluorophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[3-Bromophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[naphth-1-yl]-urea,  
N-[2,6-Dichlorophenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-Chloro-2-methylphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-Bromo-3-methylphenyl]-N'-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-2-nitrophenylacetamide,  
4-Bromo-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-4-biphenylacetamide,  
3,4-Dichloro-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]benzamide,  
N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]naphth-2-ylacetamide,  
4-Dimethylamino-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide.

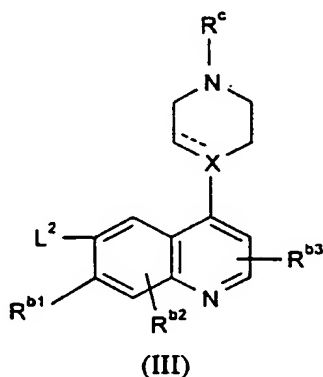
3,4-Difluoro-N-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide.  
 N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-3-phenoxyphenylacetamide.  
 N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylcarboxamide,  
 N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-4-phenoxybenzamide,  
 N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl]-  
 urea,  
 N-[4-(4-Methylpiperazin-1-yl)quinolin-6-yl]-N'-[5-oxoindan-2-yl]-urea,  
 2,3-Dihydro-8-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-  
 naphthalenyl)aminocarbonyl]pyrrolo[2,3-g]quinoline,  
 9-(4-Methylpiperazin-1-yl)-1-[(5-oxo-5,6,7,8-tetrahydronaphth-6-yl)aminocarbonyl]-1,2,3,4-  
 tetrahydropyrido[2,3-g]quinoline  
 or pharmaceutically acceptable salts thereof.

10. A process for the preparation of a compound of formula (I) which comprises:

(a) where L is -C(=O)-DG - or -DG-(C=O)-, coupling a compound of formula (II):

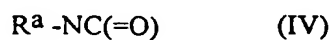


with a compound of formula (III):

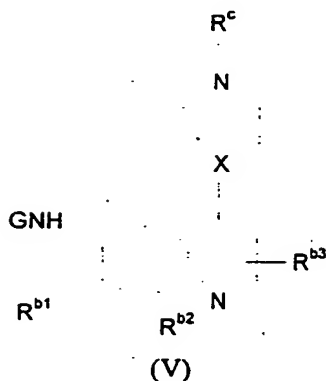


in which  $\text{R}^a$ ,  $\text{R}^{b1}$ ,  $\text{R}^{b2}$ ,  $\text{R}^{b3}$ ,  $\text{R}^c$  and X are as defined in formula (I) and  $\text{L}^1$  and  $\text{L}^2$  contain the appropriate functional groups which are capable of reacting together to form the L moiety; or

(b) where L is -Y-C(=O)-DG in which D is nitrogen and Y is NH, coupling a compound of formula (IV):

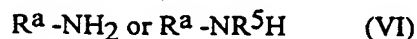


in which  $R^a$  is as defined in formula (I) or a protected derivative thereof, with a compound of formula (V):



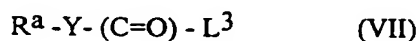
in which  $R^{b1}$ ,  $R^{b2}$ ,  $R^{b3}$ ,  $R^c$ , G and X are as defined in formula (I), or a protected derivative thereof; or

(c) where L is - Y - C(=O) - DG - in which D is nitrogen and Y is NH or  $NR^5$ , reacting a compound of formula (VI):



in which  $R^a$  and  $R^5$  are as defined in formula (I) with a compound of formula (V) together with an appropriate urea forming agent; or

(d) where L is - Y - C(=O) - DG - in which D is nitrogen and Y is  $CH_2$  or O, reacting a compound of formula (VII):

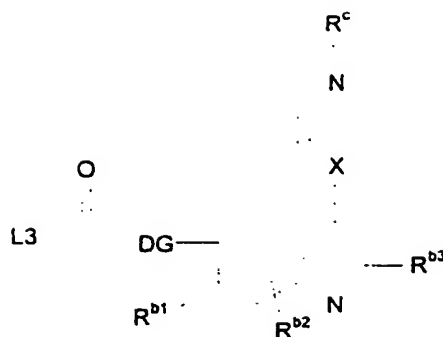


in which  $R^a$  is as defined in formula (I), and  $L^3$  is an appropriate leaving group, with a compound of formula (V); or

(e) where L is - Y - C(=O) - DG - in which D is CH and Y is NH, reacting a compound of formula (VI):



in which  $R^a$  is as defined in formula (I) with a compound of formula (VIII):



(VIII)

in which G, X, R<sup>b1</sup>, R<sup>b2</sup>, R<sup>b3</sup> and R<sup>c</sup> are as defined in formula (I) and L<sup>3</sup> is an appropriate leaving atom;

and optionally thereafter:

- removing any protecting groups,
- converting a compound of formula (I) into another compound of formula (I),
- forming a pharmaceutically acceptable salt.

11. A compound according to any of claims 1 to 9 for use in therapy.

12. A compound according to any of claims 1 to 9 for use in the treatment of depression.

13. A pharmaceutical composition which comprises a compound according to any of claims 1 to 9 and a pharmaceutically acceptable carrier.

# INTERNATIONAL SEARCH REPORT

In .ational Application No

PCT/EP 98/07804

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D401/12 A61K31/47 C07D215/42 C07D215/46 C07D413/12  
A61K31/505 C07D471/04 //(C07D471/04,221:00,209:00),  
(C07D471/04,221:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 32967 A (SMITHKLINE BEECHAM PLC) 7 December 1995 see the whole document ---	1-13
X	WO 97 07120 A (SMITHKLINE BEECHAM PLC) 27 February 1997 see the whole document ---	1-13
E	WO 99 07700 A (SMITHKLINE BEECHAM PLC) 18 February 1999 see the whole document ---	1-13
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

27 April 1999

Date of mailing of the international search report

14/05/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Hartrampf, G

# INTERNATIONAL SEARCH REPORT

In International Application No

PCT/EP 98/07804

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>SCHOEFFTER P. &amp; HOYER D.: "Interaction of arylpiperazines with 5-HT1A, 5-HT1B, 5-HT1C and 5-HT1D receptors: Do discriminatory 5-HT1B receptor ligands exist?"</p> <p>NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY, vol. 339, no. 6, 1 June 1989, pages 675-683, XP000576360</p> <p>---</p>	1-13
A	<p>STARKEY S.J. &amp; SKINGLE M.: "5-HT1D as well as 5-HT1A autoreceptors modulate 5-HT release in the guinea-pig dorsal Raphé nucleus"</p> <p>NEUROPHARMACOLOGY, vol. 33, no. 3/4, 1994, pages 393-402, XP000654898</p> <p>---</p>	1-13
A	<p>PAUWELS P.J. &amp; PALMIER C.: "Functional effects of the 5-HT1D receptor antagonist GR 127,935 at human 5-HT1D.alpha., 5-HT1D.beta., 5-HT1A and opossum 5-HT1B receptors"</p> <p>EUROPEAN JOURNAL OF PHARMACOLOGY. MOLECULAR PHARMACOLOGY SECTION, vol. 290, no. 2, 1995, pages 95-103, XP000612639</p> <p>-----</p>	1-13

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/07804

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9532967 A	07-12-1995	AU 2565595 A EP 0763034 A JP 10500960 T US 5756496 A ZA 9504330 A	21-12-1995 19-03-1997 27-01-1998 26-05-1998 17-05-1996
WO 9707120 A	27-02-1997	NONE	
WO 9907700 A	18-02-1999	NONE	